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THE AMERICAN REVIEW OF TUBERCULOSIS

JOURNAL OF
THE NATIONAL TUBERCULOSIS ASSOCIATION

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VOLUME XXXVIII
JULY-DECEMBER, 1938

PUBLISHED MONTHLY
AT MT. ROYAL AND GUILFORD AVENUES, BALTIMORE, MD.
BY THE NATIONAL TUBERCULOSIS ASSOCIATION

10998

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THE SKIN AS AN ORGAN OF EXPERIMENTAL TUBERCULOUS INFECTION[1]

HENRY SEWALL[2] AND GERALD DUFFNER

The question whether allergy favors, opposes or has nothing to do with the development of specific immunity in tuberculosis still invites experimental investigation. The analysis of this subject is fraught with many difficulties, among which is the fact that there has always been a lack of correlation between the amount of bacilli injected and their effect. Thus, when guinea pigs are inoculated with a virulent strain of human bacilli and examined postmortem after three or four months, there is a lack of quantitative relationship between the effects of a large range of doses and the extent of the lesions produced. The pathological lesions may fail to discriminate strongly between two infections, of which one follows an inoculation a thousand times as great by weight as the other.[3]

The mind irresistibly tends to unite associated facts in a teleologic story which maintains its qualitative features whichever of two opposing

[1] From the Laboratories of the National Jewish Hospital, Denver, Colorado.

[2] At the time of his death, the late Dr. Henry Sewall with the help of his assistant, Mr. Gerald Duffner, was engaged in this study. The experiments were nearly completed and Dr. Sewall had started to analyze the results. Mrs. Sewall has entrusted to me, with the help of Dr. Esmond R. Long, the pleasant duty of preparing this paper for publication. The result is necessarily far less adequate than if Dr. Sewall had completed the work himself. He had written the introduction and had prepared a general outline for the paper, but the evaluation of the observations and the discussion of the implications of the experiments need Dr. Sewall's rich experience with the problem of immunity in tuberculosis. Since all of the data of his experiments were not available, and on account of the need of checking certain points with sections, we have repeated the experiment at the Rockefeller Institute with a small group of animals. Our results confirmed Dr. Sewall's observations and, through the stimulus of the plans which Dr. Sewall had in mind but had not yet carried out, we have been led to further studies, especially on the relation of intracutaneous injections to the lymphatic vessels. This is as Dr. Sewall would have wished and these observations will be published subsequently.—*Florence R. Sabin*

[3] This difficulty which has hampered all experimental work in tuberculosis has now been surmounted, or certainly minimized, by the studies of Dr. Kenneth C. Smithburn. He has shown that undissociated cultures of tubercle bacilli are mixtures of virulent and attenuated organisms, so that no two animals in any experiment get even approximately the same dose of the kind of tubercle bacilli that are effective in producing the disease. This work appeared in the AMERICAN REVIEW OF TUBERCULOSIS, 1937, *36*, 637, 659 and 673.—*Florence R. Sabin*

mechanisms is given the salient central position. It seems important that discrete facts deduced from events occurring spontaneously or established artificially continue to be assiduously collected and arranged in a way to establish their inevitable sequence and hence a meaning.

It is now generally accepted through the work of Krause (1), Krause and Willis (2), and Willis (3) that tuberculo-sensitive tissues specifically resist, through some surface change, the movement of tubercle bacilli in contact with them. But whether such an immune reaction is essentially harmless for the germs, or involves varying degrees of damage to the bacilli, as believed by Rist, Léon-Kindberg and Rolland (4) and Rist and Rolland (5), is still obscure.

No one familiar with clinical tuberculosis will dispute that the spread of early active tuberculosis is hastened by physical exercise and that exercise without limitation tends to produce florid disease. When X-ray evidence is available, the pathological conflagration may be revealed in a clouding of the vicinity of the focal disease which may be interpreted as vascular congestion. This was illustrated by a case studied by Sewall and Allen (6) and by Sewall (7), with repeated X-rays, in which for a term of years there was a marked allergic response to exertion with, however, ultimate recovery.

While this pathological evidence of progression of disease under muscular exercise is admitted, the seeker would know, under rest, a management which averts the congestive inflammation from exercise, what, if any, change in tissue immunity, that is, in host resistance, takes place. Do the tissues become more or less susceptible to invasion of the disease or do they remain unchanged? This would seem to be a fundamental question for the clinician and one open to experimental enquiry on susceptible animals.

Experimental evidence is already available indicating that there are changes in host resistance which can be definitely correlated with the time factor of reinoculation after the primary inoculation. For some years experimental work upon guinea pigs, using as infecting agents virulent cultures of tubercle bacilli (human strain), has been carried on in this laboratory with the object of eliciting and manipulating certain immunological reactions. In several series of experiments it was found that in animals maintained in cages under good conditions until exitus from disease, or up to a period approaching two years, there was frequently a notable difference in the extent of floridity of disease in animals receiving a second dose, reinfection or superinfection, ac-

cording to the length of the resting interval elapsing after the first dose, as contrasted with controls submitted to but one infection. In short, it appeared frequently that animals kept in quiescent condition and subjected to reinfection with large doses of bacilli lived longer and showed a markedly greater tendency to progress in healing than those which had received a single small dose of bacilli. Also a rather noticeable difference in length of life and evidence of healing pertained to the time interval between the primary and the secondary infections. The optimum interval seemed to range between 70 and 90 days, while 50 days or less led, as a rule, to more active disease and more acute pathology (8a, b).

Corresponding to these differences in tissue resistance, there appeared in the relatively small number of cases compared a well-marked gradation in the violence of the local signs of allergy noted at the site of reinoculation. When this was performed before 50 days, there was a relatively violent local reaction, redness and swelling and pain on motion of the area of infection. This was decidedly less marked when reinfection was deferred for 74 days and still less in 90 days. Thus, the allergic response was inverse to the tissue immunity and the healing fibrosis. Far from assuming a physiological antagonism, however, between allergy and resistance, we were led to see in allergy a more or less host-protective, local response to specific irritation. A similar reactive capacity is conferred upon all the tissues during a process of specific sensitization. It is the most superficial expression of the development of the teleologic mechanism of specific immunity. The efficiency of the teleologic function is developed by appropriate dosages with antigen through a considerable period of time. The more efficient the mechanism the less waste is manifested in chemical and vascular excitements. Therefore, when the important tissue strongholds are ill-protected early in the course of immunization, then the skin reaction to antigen is vigorous with florid vascular changes. When the general tissue mechanism has been trained by the development of antibodies or other salient, then there is no need for violence to hinder the introduction of dangerous antigens. Thus, as we (8a, b) have argued before, we regard the development of tuberculoimmunity as an ordeal of sensitization requiring time with attention to dosage and the intervals between doses.

Besides these important changes in host resistance due to differences in time between primary and secondary infections, clinical experience gives ample evidence of differences in tissue resistance associated with

location. Thus the dictum of Krause (9), "Within the same body, foci in one organ will be healing as those in another part are showing signs of floridity." This phenomenon was amply illustrated in the case of Sewall and Allen cited above (6), in which a cavity, probably originating around a Ghon node, showed repeatedly intense allergic excitement following exertion, and then subsequently healed and did not break down again when subsequently a fresh focus of infection developed in the other lung. This case suggests clearly that there may develop in areas around a primary focus a greater tissue resistance than exists in other parts of the body. This observation, susceptible of experimental analysis, forms the basis of the present work.

In a careful study of the sequence of events following primary inoculation with tubercle bacilli (8a), it became clear that by daily careful palpation of an inoculated area one could confirm completely the original observations of Koch that, following the subsidence of the swelling due to the inoculation itself, there is almost no sign of the inoculation beyond a slight puffiness of the skin until the development of the primary nodule. Koch's description is that, first, in the course of from 10 to 14 days there is formed *ein hartes Knötchen* which soon breaks open and until the death of the animal forms an ulcerating place. The senior author has before laid stress on the fact that careful observation and palpation enable one to discriminate quite sharply between three phenomena taking place in an inoculated area; first, vague changes that may be considered as of a general inflammatory nature, involving oedema and congestion, second, the true tubercle both before caseation and just as caseation starts, and third, the swelling due to the involvement of the regional lymph nodes (8a).

In accordance with these ideas, a restudy of the Koch phenomenon in guinea pigs was undertaken, using intracutaneous inoculations and double reinoculations, to see if one could detect a difference in the immune reactions of the tissues close to the area of the primary inoculation and far from it on the opposite side of the body in an area of different lymphatic drainage. It was thought also that the intracutaneous route of inoculation might make the reactions easier to follow since they would be more superficial.

PLAN OF EXPERIMENT

The plan of the experiment was as follows: Groups of young male guinea pigs were given a primary intracutaneous inoculation in the lower

right groin of 0.01 mgm. of a virulent human strain of tubercle bacilli suspended in 0.1 cc. of 0.9 per cent saline. The microörganisms were of the same strain used in previous experiments, namely, the Tbc G strain of Doctor Corper. They had been grown on Petroff's gentian-violet medium for about three weeks. The guinea pigs had been bred for many generations in this laboratory; they were taken in lots of twenty, with an average weight of from 250 to 300 grams. They were carefully shaved or had the hair clipped the day before. Extreme care was taken not to damage the skin. Twenty guinea pigs were inoculated at a sitting. Subsequently other groups of twenty were started. The evolution of the primary lesions was followed and at different periods the groups of twenty guinea pigs were sorted into groups of five to be reinoculated at four periods, at 26, 50, 90 and a second series at 90 days. The bacillary suspensions for the reinfections had a strength representing a weight of 0.000,1 mgm. of microörganisms per 0.1 cc. of saline.

The secondary inoculations were made in the lower right groin about 1 cm. distant from the edge of the primary ulcer and on the left side high on the abdominal wall near the lower border of the ribs, about 2 cm. from the midventral line. Thus the two secondary injections were not only separated widely on opposite sides of the body, but the predominant lymphatic drainage was caudad on the right and cephalad on the left, with pathological implications by no means identical.

After the secondary nodules following the treatment described had passed through fairly definite phases of change, a third series of intracutaneous bilateral but quadruple inoculations was made. These were definitely situated with respect to the preceding inoculations and designated by the letters A, B, C and D. Each of the tertiary inoculations was made with the dose of 0.000,05 mgm. of bacilli, that is, half the dose of the secondary inoculations. A was injected into the skin on the right side, 2 to 3 cm. to the right of the midline high on the abdomen or over the lower ribs. B was injected on the outer right groin, 2 to 3 cm. to the outer side of the nodules already present. On the left side, C corresponded to A but care was taken to place it outside, that is, lateral to the left secondary nodules already present. D found an unoccupied area in or to the outside of the left groin. Thus we were provided with two secondary and four tertiary nodules, all definitely distinguished, traceable from their inception to autopsy. The tertiary reinfections, A to D, were usually applied to only a part of the pigs in each group, the rest serving as controls. The interval between the secondary and the tertiary inoculations varied between 24 and 88 days.

RESULTS

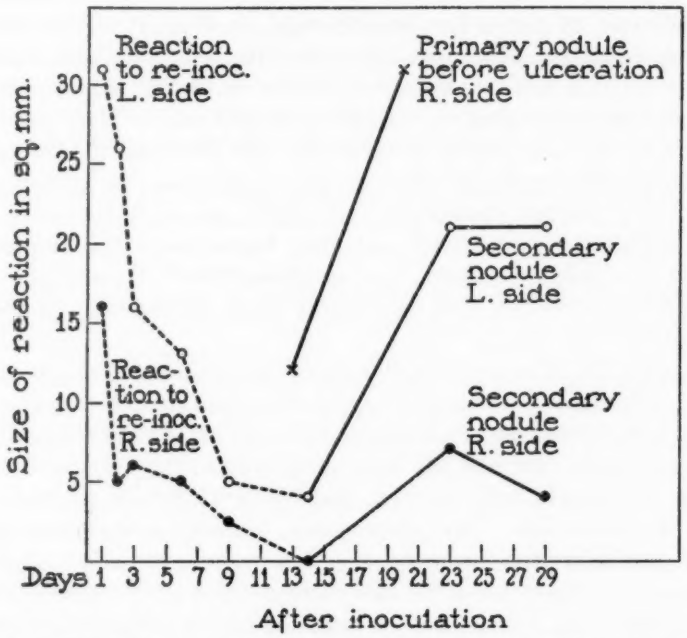
There is some evidence that there are differences in reaction to a primary inoculation according to location. Visualization of experimental reactions over an extensive anatomical surface accentuates specificities of topographical responses to the same infection. Thus, in previous work, the senior author (8a) stressed the fact that, following subcutaneous inoculation with tubercle bacilli, the resulting primary nodule, after becoming abscessed and ulcerating, apparently always tunneled a path to find an outlet through the skin. Even if the needle carrying the infecting suspension discharges it into or under the thin *panniculus carnosus* muscle which invests most of the body wall in the guinea pig, the abscess burrows outward, not inward toward the body cavity. This procedure was given interesting teleological interpretation. The inoculations on which this hypothesis was ventured were all made through the skin of the inguinal region.

For the present study a primary inoculation was made in one guinea pig in the upper left abdominal surface in the location to be used for one of the secondary inoculations. In this area the reaction showed certain differences from those to which we have become accustomed with inoculations in the right groin. The primary nodule ulcerated and discharged through the skin by an insignificant ulcer. The autopsy performed several weeks later showed that the ulceration broadly penetrated the muscular coats of the abdominal wall to the parietal peritoneum, where it was checked, but the inner surface of the peritoneum was covered with a multitude of tiny, transparent tubercles spreading to both sides of the serous sac.

In another animal, on the other hand, the drainage of the bacilli from a left upper abdominal inoculation was toward the axillary nodes, comparable to the usual drainage in the right groin. In this animal two primary inoculations were made, one in the right groin and the other, as indicated, in the upper left abdominal wall. The dose was 0.000,01 mgm. Both of these inoculations followed about the same course; both showed a slight reaction which was visible for three days. These reactions subsided completely until the fourteenth day, when the primary nodules were easily felt at both points of inoculation. By the twenty-fourth day both nodules had ulcerated and by the sixty-eighth day both had healed. At autopsy, on the seventy-sixth day, there was inflammatory tissue with small tubercles under the zones of both healed ulcers and the right inguinal and left axillary lymph nodes were equally

involved. In no instance of double secondary inoculations were the left axillary nodes as large and as extensively caseous as were the right inguinal nodes.

The data on the size of the reactions to reinoculation are given from the experiment done at The Rockefeller Institute. Ten guinea pigs were used, of which eight were reinoculated in two places, right inguinal and left axillary. The dose of the primary inoculation was 0.01 mgm. of microörganisms, strain



GRAPH 1. Showing the mean size of the reactions in sq. mm. to primary inoculation and to reinoculation at points near (right inguinal region) and remote (left axillary region) from the primary zone in eight guinea pigs. The dotted lines represent the immediate effect of reinoculation; the solid lines represent the definitive tuberculous nodules.

H37, given intracutaneously in 0.1 cc. saline. The reinoculations, which were made with the same strain after 90 days, contained 0.000,05 mgm.

In one of these guinea pigs, the primary nodule was excised under an anaesthetic 14 days after inoculation. The wound healed promptly and no ulcer developed. Sections of the excised nodule showed an intracutaneous tubercle which measured 4 mm. in diameter. It had not started to caseate; every epithelioid cell was intact and there was a considerable infiltration with neutrophilic leucocytes. Sections stained for tubercle bacilli showed about 60 per oil-immersion field. For a considerable time, the right inguinal nodes

in this animal were smaller than those in the other animals of the series, and when the animal was sacrificed, only about half of the node had been destroyed by caseation. This animal was not reinoculated and was killed 91 days after the primary injection.

All of the animals that had the two secondary inoculations showed about the same immediate response. These reactions are indicated in graph 1, taken from the fused measurements of the zone of reaction. In 24 hours there was an area of redness and oedema, the extent of which was in each instance larger on the left side than on the right. The zone of these reactions is indicated by dotted lines on the graph, in which it will be seen that the amount of reaction, which was like a tuberculin test, was slight, measuring less than a one-plus test, but definitely greater on the left side remote from the primary inoculation than on the right side near to it. These early reactions faded in the same time as a tuberculin test and none of them showed any necrosis. The three solid lines on the graph show the growth of the nodules of the primary inoculation and of the two secondary ones. The secondary nodules appeared later and grew more slowly than the primary ones; unlike the primary nodules, they never ulcerated. As with the immediate reaction, the nodules were consistently larger remote from the primary inoculation.

The data on the chart showing differences in reaction of the right and left sides were submitted to a statistical analysis and in the main proved significant; that is, the differences were significant in six out of eight animals. The differences between right and left sides apply only to the times indicated on the graph, for subsequently multiple nodules developed on the right side, reversing the proportion. This phenomenon, probably related to lymphatic drainage, must be studied further.[4]

The absence of ulceration of the skin corresponding to the zones of reinfections we interpret as a restriction of caseation in the secondary nodules, as shown in sections. In none of the tubercles of reinfection were tubercle bacilli found in such numbers as in the primary nodules excised for study. Moreover, many of the bacilli found in them were of the beaded type described by Sewall in 1891 (10) for bacilli of degraded virulence.

SUMMARY

These studies demonstrate that the first reaction to reinfection, which is like a tuberculin test, is slightly less in the immediate vicinity of a primary inoculation than at a considerable distance from it. This

[4] In a subsequent experiment, four guinea pigs inoculated intracutaneously all showed accessory subcutaneous tuberculous nodules after an interval of four months.—*Florence R. Sabin*

indicates that the tissues around the primary zone are less allergic than elsewhere. The early reactions fade as in a tuberculin test. The subsequent nodules of the reinfection are also, for a time, smaller near the primary inoculation.

These investigations, then, show that just as in clinical tuberculosis, so also in the experimental disease in animals, there are differences both in allergic responses and in the evidences of tissue resistance in different parts of the body.

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ALLERGIC AND DESENSITIZED GUINEA PIGS[1,2]

A Study of Factors Bearing upon the Problem of Immunity in Tuberculosis

HENRY STUART WILLIS, C. EUGENE WOODRUFF, RUBY G. KELLY AND MARIE VOLDRICH

Animal experiments involving the therapeutic use of tuberculin fall roughly into two groups—those in which relatively small doses of tuberculin have been employed and those in which the tuberculin dosage has been pushed to the point of completely desensitizing the experimental animal. Numerous experiments of the first type have demonstrated that the tuberculous animal eventually becomes tolerant of repeated small doses of tuberculin or killed tubercle bacilli. Weinzirl and Bohart (1) pioneered in this type of experiment in America. Using broth-culture filtrate, a tuberculoprotein and, finally, tubercle bacilli killed by various chemicals, they were able to reduce considerably the skin reactivity of tuberculous guinea pigs. According to them the optimal time interval for giving doses of the desensitizing agent is about seven days.

De Savitsch and coworkers (2) combined viosterol and tuberculin in the treatment of tuberculous guinea pigs and noted "definitely beneficial results." The largest dose of tuberculin used by these workers was 1.0 mgm. per animal per week. There is no record concerning what degree of desensitization (if any) was produced.

Derick, Branch and Crane (3) used heat-killed and formol-killed bacilli as well as a bacillary suspension and a tuberculoprotein. With the relatively small doses employed many of their tuberculous animals became skin-test negative to 0.1 cc. of 1:10,000 tuberculin though they were "markedly hypersensitive" when tested with 0.1 cc. of 1:20 tuberculin. The authors noted a prolongation of life over the controls in the animals treated with the heat-killed bacilli.

In guinea pigs which had been infected with tubercle bacilli of low virulence Branch and Kropp (4) used the intravenous route for adminis-

[1] From the Wm. H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Michigan.

[2] Presented in part at a session of the Pathological Section at the 33rd annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, June 1, 1937.

tering broth-culture filtrate. The dose of the filtrate reached 1 and then 2 cc., given, during the latter part of their experiment, at weekly intervals. Their treated animals showed "markedly less tuberculosis than the controls."

Manaud (5), in 1909, presented the first experiment which we have been able to find of the second type, involving the use of relatively large doses of tuberculin or tuberculin products.[3] Employing a *tuberculine précipitée* Manaud "accustomed" some of his infected pigs to as much as 200 mgm. of the tuberculin, while a dose of 20 mgm. killed the allergic animals. He reported that all of the tuberculous guinea pigs which received the large doses of tuberculin succumbed more quickly than the remainder and presented more extensive lesions. In summary he stated that, in the tuberculous guinea pigs "accustomed" to receive enormous doses of tuberculin, the tuberculosis evolved more rapidly than in the control animals.

In 1929, Rich and McCordock (7) suggested that tuberculin therapy, to be effective, must proceed to the point of desensitization to tuberculoprotein and the disappearance of allergic response. In a later paper Rich (8) discussed further the problems of desensitization in tuberculosis, though most of his experimental work was performed with microorganisms other than the tubercle bacillus. In 1934, however, appeared a paper from Rich's laboratory (9) describing the complete desensitization of allergic guinea pigs. In this experiment Rothschild, Friedenwald and Bernstein, starting with a minute dose, were able eventually to give their tuberculous pigs a daily subcutaneous dose of 2 cc. of undiluted Old Tuberculin. The animals lost their skin sensitivity completely. After infection of the desensitized animals with virulent tubercle bacilli, these workers concluded that "complete desensitization does not deprive the treated animals of any aspect of their immunity as measured by the course and severity of local lesions, by the spread and severity of their visceral lesions, and by the mortality from tuberculosis in infected animals." It should be noted here that all of Rothschild's animals were sacrificed by the 65th day after the virulent infection.

In the same year that the above work appeared, Cummings and Delahant (10) reported that the daily administration of at least 0.25 cc. of undiluted Old Tuberculin to guinea pigs infected with avirulent tubercle

[3] Burnet (6), in 1908, reported the desensitization of tuberculous guinea pigs with precipitated tuberculin. He made no study, however, of the effect of desensitizing on the disease process.

bacilli prevented them from developing allergy. Subsequent inoculation of these desensitized animals with virulent tubercle bacilli led Cummings and Delahant to the conclusion that "the suppression of hypersensitiveness to tuberculin can be successfully accomplished in tuberculous guinea pigs without interfering with the immune response to reinfection." It should be noted that in this work, too, the animals were sacrificed a relatively brief while (6 weeks) after the virulent inoculation.

For upwards of five years we have been carrying out experiments on the general question of desensitization of tuberculous guinea pigs. Several brief progress reports of this work have been made (11) and we wish now to give, in more or less categorical manner, the sequence of events in these experiments. The more strictly pathological features of the work have been published elsewhere (12).

TECHNIQUE

The guinea pig, being the animal of choice in experiments which involve the allergic manifestations of tuberculosis, has been used exclusively. In our first two experimental series guinea pigs of different colors were employed. However, from these and from previous experiments, we have gained the impression that albino guinea pigs react more uniformly to a given dose of tubercle bacilli than do pigs of mixed colors, so we have used albino pigs in all our recent experiments. The pigs for a given experimental series were obtained at the same time from one supply house. At the time of inoculation the animals were from 250 to 300 grams in weight.

Through the use of albino guinea pigs of approximately the same size we feel that the element of individual variation in resistance has been reduced to a minimum. The other variable, dosage, was carefully controlled. All animals in a given series were inoculated at the same time from the same suspension of bacilli. Our suspensions, made up after careful trituration of a weighed amount of bacilli, contained microscopical clumps of the microörganisms. However, if sedimentation of bacilli is guarded against, the presence of small clumps does not militate against getting a uniform inoculation. Our procedure was to agitate the inoculum in its containing vessel by forcing a few cubic centimeters of the fluid into and out of the syringe. Then sufficient inoculating fluid for only one animal at a time was taken into the syringe and immediately injected into the subcutaneous tissue. This technique avoided the sedimentation which can be seen grossly if the inoculum for several animals

is taken into the syringe at one time. In a smear of the inoculating fluid used for the first one of a series of 50 guinea pigs approximately the same density of bacilli was found as in a similar smear of the fluid used for the fiftieth animal.

In all except the first of our experiments the microörganism used for the virulent inoculation was our "G" strain of human type tubercle bacillus, an organism of known high virulence.

THE DESENSITIZATION OF ALLERGIC GUINEA PIGS

Experiment 1

September 2, 1932: Eighty guinea pigs were given a sensitizing infection with the avirulent R1 strain of tubercle bacilli, each animal receiving a subcutaneous dose of 0.5 cc. of a milky suspension of the bacilli. Seven weeks later the pigs showed a positive tuberculin reaction to 0.1 cc. of 2 per cent OT. They were divided into two groups, 72 to be desensitized and 8 to be left allergic.

October 27, 1932: Tuberculin therapy[4] was instituted on the 72 allergic pigs and on 9 normal pigs, starting with 2.5 mgm.[5] of OT given subcutaneously. From this amount the dosage was increased cautiously until, in five and one-half weeks' time, each animal received a daily dose of 1 cc. of undiluted OT. During this period there was a 47 per cent mortality amongst the animals receiving tuberculin, while none of the animals left allergic died.

December 6, 1932: The remaining desensitized animals showed no reaction to 0.1 cc. of 2 per cent OT given intracutaneously. Because of the high mortality in this group the tuberculin dosage was dropped to 0.2 cc. daily and maintained at that level during the remainder of the experiment.

December 13, 1932: The three groups of animals were inoculated in the left groin with virulent tubercle bacilli, each animal receiving a subcutaneous dose of 0.01 mgm.

February 7, 1933: The remaining pigs were given the Mantoux test, using 0.1 cc. of 2 per cent OT. The reactions, read after 48 hours, showed the 8 allergic pigs with a high degree of skin sensitivity. Most of the pigs in the allergic-desensitized group (now receiving 0.2 cc. of OT daily) showed some return of skin sensitivity. The normal-tuberculinized animals were skin-test negative.

[4] The 12 liters of tuberculin used in our various experiments was very kindly furnished by Parke, Davis & Company of Detroit.

[5] That is, 0.0025 cc. of Old Tuberculin.

February 11, 1933: Experiment terminated. Up to this date 42 of the 72 pigs in the desensitized group had died, a total mortality of 58 per cent, while none of the 8 pigs left allergic had died. Two of the 9 normal-tuberculinized and infected pigs had died.

Postmortem findings: Spontaneous death in the desensitized animals was due to either pneumococcus pneumonia or extensive cellulitis which involved much of the skin in the region where tuberculin had been injected. The findings in the sacrificed animals were as follows:

Allergic: All 8 animals showed enlarged inguinal lymph nodes, with caseation in two instances. Two of the animals showed tubercles in the spleen but none of the other animals showed dissemination of the infection.

Allergic-desensitized: The 30 remaining pigs in this group showed enlarged inguinal lymph nodes, with caseation in 5 instances. In 10 animals there were scattered tubercles in the lungs and in 3 tubercles in the spleen.

Normal-tuberculinized or "normal-desensitized": These animals, which had developed but little allergy during the course of their infection, showed the most extensive disease. Seven came to the final postmortem examination. In each animal the inguinal lymph nodes were enlarged, caseation being evident in 5 instances. In 6 animals the spleen and lungs showed some tuberculosis. Four pigs showed scattered tubercles in the liver.[6]

Comment: In general, our experience with the desensitization of guinea pigs can best be described by quoting from Rothschild and coworkers (9):

> The mere problem of keeping a group of guinea pigs alive for six months during which they are subjected to daily injections presents no small difficulty. We found that if the desensitizing doses of tuberculin were increased too slowly, most of the animals died of causes other than tuberculosis before desensitization was completed. On the other hand, if the dose of tuberculin is increased too rapidly, the animals became dehydrated and malnourished. . . . In the first experiment, only 8 per cent of the tuberculin-treated animals survived the period of desensitization and were available for inoculation with virulent organisms. . . . In the final experiment, 50 per cent of the tuberculin-treated animals reached the virulent inoculation and 30 per cent of these survivors lived for two months after their infection with virulent bacilli.

It will be noted that in our own experiment 47 per cent of the desensitized animals died before reaching the virulent inoculation compared

[6] In the experimental series to be described later the liver and spleen of the desensitized animals showed no gross tuberculosis. The liver and spleen lesions in the present series are probably due to the relatively small dosage of tuberculin given to these animals following the virulent inoculation.

with 50 per cent quoted above. We observed further that the animals first to succumb during the period of desensitization were invariably the smallest and weakest in a given group. Our experience indicates that the weeding out which takes place among the allergic animals during desensitization is a prime example of "survival of the fittest." After 47 per cent of our guinea pigs had died during desensitization, the remaining animals were the *best* ones of the original group. This fact must be given consideration when comparing the reaction of groups of desensitized and allergic guinea pigs to infection with virulent tubercle bacilli. If the desensitizing mortality has been high, the remaining animals represent a select group, while the allergic group, in which there has been little or no mortality, is unselected.

Experiment 2

Experiment 1 showed the high mortality which may occur when allergic guinea pigs are desensitized. This mortality may have been due in part to the fact that the experiment was carried through the winter in a room in which the heating arrangements were not entirely adequate. We have noticed repeatedly that guinea pigs receiving tuberculin are much more susceptible to temperature changes than are the allergic animals in adjacent cages. In our second experiment the animals were kept in a warmer room. Moreover, the desensitizing dose was increased more rapidly in the hope that the effect of tuberculinization might be observed over a longer period of time. This proved to be the case.

In experiment 2 two separate series of animals were treated, one being started in July, 1935, and the other in November, 1936. In each series the animals were rendered allergic by means of R1 inoculation. Then, at the end of a month, when a skin test showed that the animals were allergic, the desensitizing process was started, beginning with 10 mgm. of tuberculin. In both of the series the desensitizing dose was increased in four weeks to 1 cc. of undiluted OT at which time the animals were found to be skin-test negative to 10 mgm. of tuberculin. At this point, approximately one month after desensitization had been started, the animals in both series were inoculated with 1 mgm. of virulent human type tubercle bacilli, strain G. The daily desensitizing dose of 1 cc. of tuberculin was continued.

In our two experimental series 20 allergic animals were used, 20 normal controls and 20 allergic-desensitized. In addition 10 normal guinea pigs were given the same daily tuberculin doses as the allergic-desensitized group and then were inoculated with virulent tubercle bacilli at the same time as the others. For want of a better term we have named this latter group the

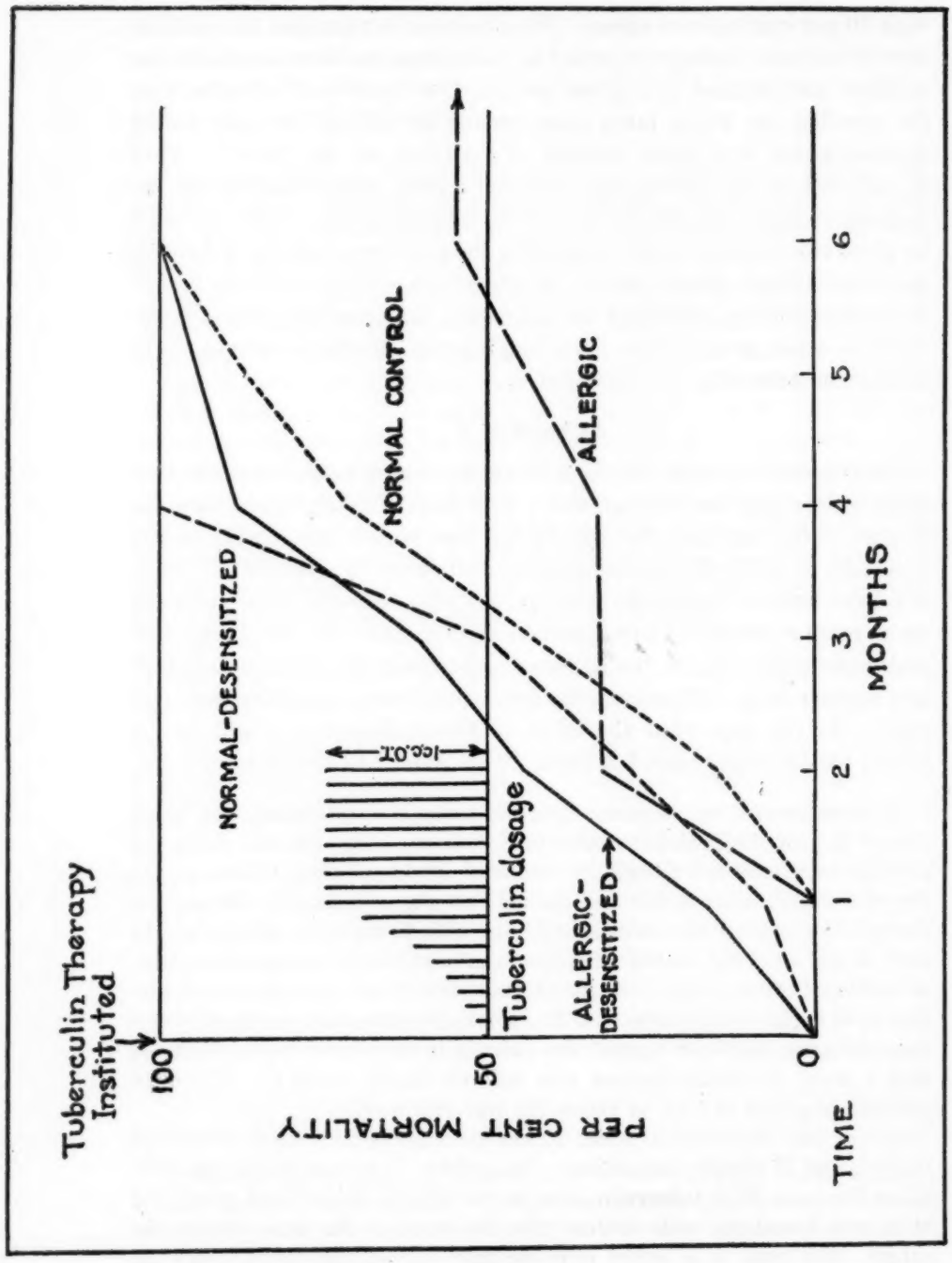

CHART 1. Mortality curves based on the mortality record of 70 guinea pigs (20 control, 20 allergic, 20 allergic-desensitized and 10 normal-desensitized). All of the normaldesensitized animals were dead by the end of the fourth month. The allergic-desensitized and the control animals had died by the end of the sixth month (5 months after the virulent inoculation). Nearly half of the allergic animals (45 per

"normal-desensitized." The data from the two experimental series are combined in chart 1.

As indicated in the chart, some of the animals in both of the tuberculin-treated groups died during the desensitizing period. Over the entire experimental period the normal-desensitized pigs fared the worst, all of these animals being dead at the end of the fourth month while some in the allergic-desensitized and normal-control groups lived until the end of the sixth month (5 months after the virulent inoculation). The initial high mortality in the allergic group is noteworthy. Seven, or 35 per cent of these animals, died during the first month following the virulent inoculation. After this first month the allergic animals fared much better. At the end of the sixth month (when all of the other animals were dead) there had been a 55 per cent mortality in this group.

Postmortem findings: The 7 allergic animals which died soon after the virulent inoculation exhibited in each case a haemorrhagic pneumonia without any gross sign of tubercle. The lesion suggested some type of allergic response to the relatively large dose of bacilli (1 mgm.) used for the secondary inoculation. Allergic animals which died during the fifth and sixth months showed tubercle in lungs and spleen along with slight involvement of the liver.

The control animals, even those which died during the latter part of the first month, showed tuberculosis of lungs, liver and spleen.

In the normal-desensitized group the animals died during the first two months due either to haemorrhagic pneumonia or cellulitis. In the third and fourth months, however, these animals showed progressive involvement of the lungs with a bronchopneumonic process, smears from which were loaded with tubercle bacilli. Frequently the lungs were so distended and hepatized as to fill the chest cavity completely. At the same time the livers and spleens of these animals showed no gross tuberculosis whatsoever.

The allergic-desensitized animals, like the normal-desensitized, died at first because of haemorrhagic pneumonia or cellulitis, continuing to die from these causes during the third month. During and after the fourth month, however, these animals developed tuberculous pneumonia without at any time showing gross tubercle in liver or spleen.

Comment: In this experimental series two findings in particular attracted our attention: First, the spleen, which in the normal guinea pig is extremely susceptible to tuberculosis, showed no gross signs of involvement in our desensitized animals. Second, the tuberculous pneumonia which developed in these latter animals was unusually extensive. Both of these observations were investigated further.

CHART 1. Mortality curves based on the mortality record of 70 guinea pigs (20 control, 20 allergic, 20 allergic-desensitized and 10 normal-desensitized). All of the normaldesensitized animals were dead by the end of the fourth month. The allergic-desensitized and the control animals had died by the end of the sixth month (5 months after the virulent inoculation). Nearly half of the allergic animals (45 per

SPLEEN CULTURES IN TUBERCULOUS GUINEA PIGS

As noted above the spleens in both the normal-desensitized and allergic-desensitized pigs appeared relatively normal at autopsy even though the lungs of the same animals might be hepatized with tuberculous pneumonia. This finding prompted us to attempt to determine the relative status of the spleens with regard to their content of bacilli. Spleen cultures were made using the technique which has been described by Lurie (13). In our two experiments of this type, 72 young albino guinea pigs were used. At the time of the virulent inoculation the animals were of three types, normal control, allergic and allergic-desensitized, the latter being kept in the desensitized state by means of daily 1 cc. injections of tuberculin. Animals of each type, sacrificed at weekly or at two-week intervals, had their spleens removed under aseptic precautions. A measured portion of the organ was ground in a sterile

TABLE 1

Number of bacilli in spleen (in 1000's)

	INTERVAL					
	1 week	2 weeks	4 weeks	6 weeks	8 weeks	10 weeks
Control	610	3,100	3,600	4,300	1,600	1,900
Allergic	0.8	1	8	1.5	1	3
Desensitized	20	40	75	160	220	300

mortar with a small amount of saline. One portion of the triturated mass was then treated with hydrochloric acid as a precautionary measure against inadvertent contamination with pyogens. The remaining portion was inoculated (in several dilutions) on tubes of Petragnani's and Löwenstein's media, six tubes being used for each dilution. Then the portion treated with acid was inoculated in similar fashion. The cultures were examined at the end of three weeks and after that at weekly intervals until three months had elapsed, the maximum number of colonies on each tube being determined. Then, knowing the total number of colonies which grew at a given dilution, and knowing the proper dilution factor, it was possible to estimate the number of bacilli in each of the spleens

The combined data from our two experiments of this type are shown in table 1. Each figure in the table (multiplied by 1000) represents a numerical average of the number of bacilli in several spleens. In the

first four columns the average is based on 5 spleens, in the last two columns on 2 spleens. As shown in the chart the count of bacilli is high in the control spleens from the first week on. The allergic-desensitized spleens, while showing a count consistently lower than the controls, are just as consistently from 10 to 100 times as high as the spleens of the allergic animals. The cultures made from 5 spleens of allergic pigs were completely negative. In another experimental series cultures were made from the spleens of a number of normal-desensitized animals. The counts indicated approximately the same number of bacilli in these spleens as in the spleens of the control animals.

The finding of large numbers of bacilli in the spleens of desentized pigs indicates that, in the desensitized animal, tubercle bacilli remain in contact with the tissues for long periods of time without giving rise to tubercle formation.

THE DEVELOPMENT OF TUBERCULOSIS IN NORMAL-DESENSITIZED GUINEA PIGS

In experiment 2 the group of animals termed normal-desensitized were of the greatest interest to us. These animals, thoroughly tuberculinized, then infected with virulent bacilli and kept tuberculinized by means of daily 1 cc. injections of tuberculin, do not develop allergy at any time. It is in these animals which have never been allergic that one can best study the effect of allergy (or lack of allergy) upon the development of tuberculosis. With this point in view two more experimental series of pigs were inoculated. One of these series has already been reported (11). For the second series 60 albino guinea pigs, weighing from 250 to 300 grams each, were employed. They were divided in groups as follows:

(*1*) Allergic: 12 pigs sensitized by means of R1 infection given 3 weeks previously
(*2*) Controls: 24 pigs
(*3*) Normal-desensitized: 24 pigs given daily 1 cc. injections of tuberculin beginning one day before the inoculation with virulent bacilli

Each animal was inoculated subcutaneously with 0.1 mgm. of virulent bacilli on May 11, 1937. After three weeks, six weeks and twelve weeks the animals were given the Mantoux test, using 0.1 cc. of 10 per cent OT. The animals in the allergic group, originally skin-test positive, remained so. The control group, with the exception of two animals, had developed skin sensi-

tivity by the end of the third week. The normal-desensitized group at no time showed a positive skin test.

In this, as in all of our experiments, the desensitized animals lost weight and muscle tone, and much of their hair fell out after the treatment had been continued for a number of weeks (figure 1). After four weeks of the tuberculin therapy (and this, again, is a characteristic finding) many of the pigs developed large cutaneous ulcers. These ulcers are probably self-inflicted for we have frequently observed the desensitized animals biting at their skin following the tuberculin injection. The mortality record for the experiment is shown in chart 2.

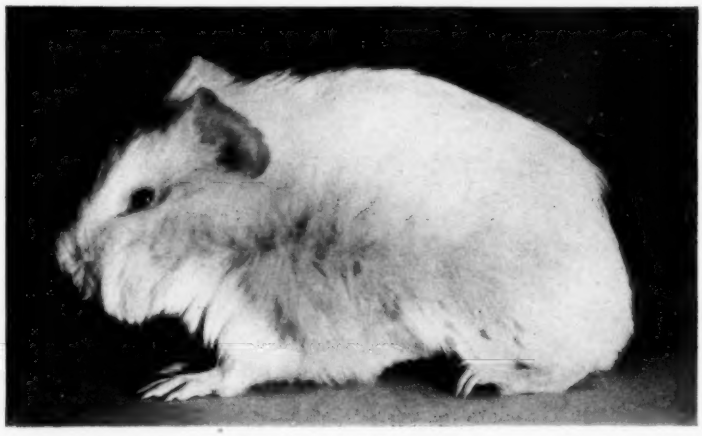

FIG. 1. Normal-desensitized guinea pig. Photograph taken 7 weeks after infection with 0.1 mgm. of virulent tubercle bacilli. The desensitized animals lose weight and muscle tone and much of their hair falls out. ($\frac{2}{3}$ natural size)

As indicated in the chart, all of the desensitized animals had died by the end of the sixteenth week. Two animals in the control group were still alive, though in very poor condition, in the twenty-first week. These two, along with two allergic pigs, were sacrificed. Nine pigs in the allergic group remain alive and in good condition at the present writing, twenty-six weeks after the virulent infection.

Postmortem findings: Control group: The four animals in this group which died during the second week were victims of an unfortunate accident. On the twelfth day after the virulent infection they were inadvertently given 1 cc. of tuberculin subcutaneously, along with the normal-desensitized group. All 4 animals were dead within 24 hours. The lungs were atelectatic and showed numerous haemorrhages, while the livers and spleens were congested. It is

MORTALITY CHART

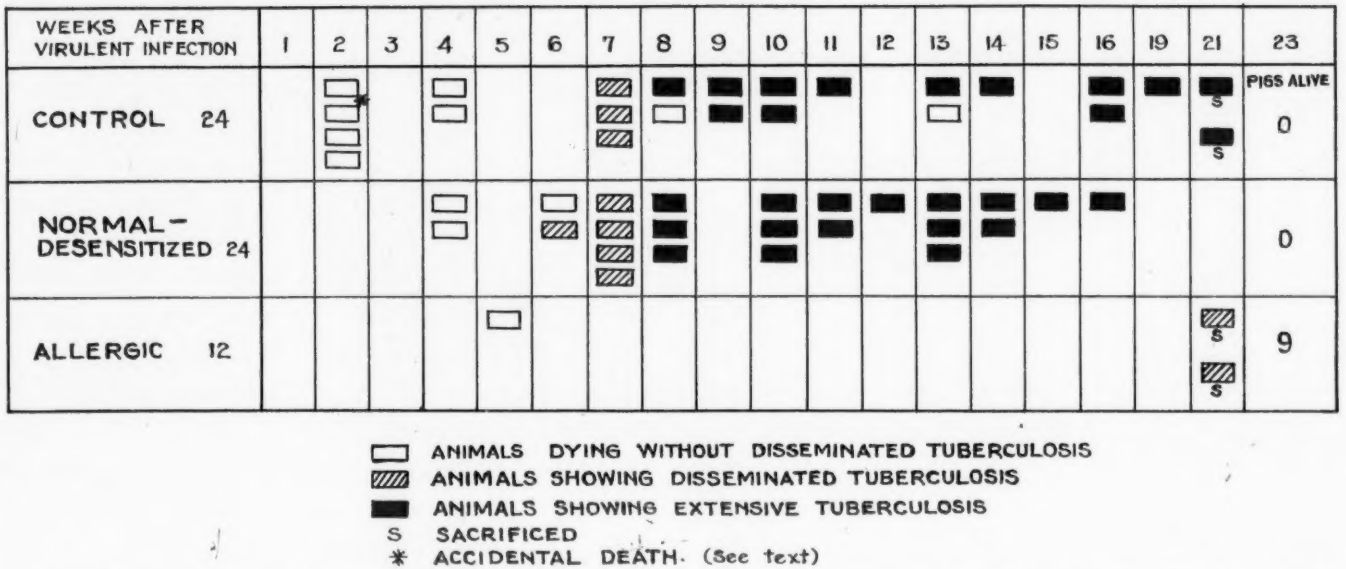

CHART 2. Mortality record for normal-desensitized, allergic and control animals. This chart is based on data from 24 control, 24 normal-desensitized and 12 allergic guinea pigs. The rectangles indicate the week in which each animal died and indicate roughly the extent of the disease. Four animals were sacrificed in the twenty-first week. At the present writing, 26 weeks after the virulent infection, the 9 allergic pigs are alive and in good condition.

FIG. 2

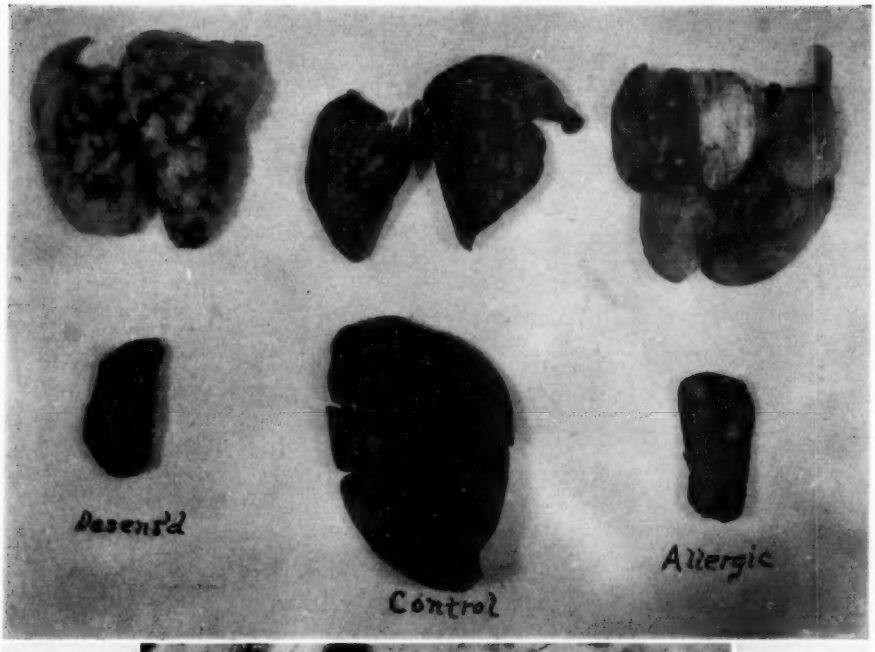

FIG. 3

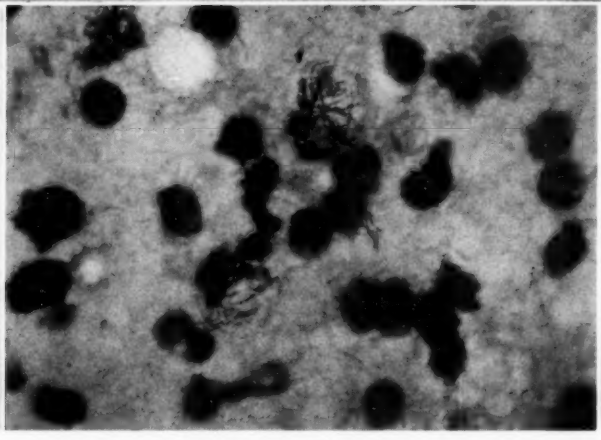

FIG. 2. Lungs and spleens of normal-desensitized, control and allergic guinea pigs. The spleen of the desensitized animal is normal in size and shows no gross tubercles while the corresponding lungs contain large areas of tuberculous pneumonia. The spleen of the control animal is greatly enlarged and exhibits extensive tuberculosis. The corresponding lungs are congested and show miliary tubercles. The spleen of the allergic animal is practically normal in size. It shows a few miliary tubercles as do the lungs. There is marked enlargement of the peribronchial lymph nodes. ($\frac{2}{3}$ natural size)

FIG. 3. Impression-smear from cut surface of lung of desensitized guinea pig. The lungs of these animals contain innumerable acid-fast bacilli, whereas acid-fast microörganisms are extremely difficult to demonstrate in the lungs of the allergic or the control pigs. Ziehl-Neelsen stain. Photograph taken with white light. × 1200

of interest that in less than two weeks' time sufficient allergy had developed to make the animals respond thus to a large dose of tuberculin. In the fourth week two more animals in the infection control group died, each showing peritonitis and slight swelling of the Malpighian bodies in the spleen. Control animals dying in the seventh week and thereafter showed tuberculosis in lungs, liver and spleen, with two exceptions. One animal which died in the eighth and one in the thirteenth week showed pneumococcus pneumonia, evidently of long duration, in one lobe of the lung. Each of these animals had failed to react to tuberculin. In each animal a caseous lymph node was found in the groin at the site of inoculation with virulent tubercle bacilli, but there was no sign of dissemination of the tuberculosis.

Normal-desensitized: In this group 2 animals dying in the fourth week and one in the sixth week showed merely a haemorrhagic pneumonia. One of the animals which died in the sixth week, as well as 4 animals which died in the seventh week, showed evidence of dissemination of the tuberculous infection in the form of miliary lesions in the lung. By the eighth week and thereafter, in all of the desensitized animals which died, these miliary lesions had expanded into areas of bronchopneumonia and, after the twelfth week, the lungs were invariably distended and hepatized by the pneumonic process (figure 2). Smears from these areas of bronchopneumonia showed innumerable acid-fast bacilli (figure 3). As in experiment 2, the livers and spleens of these desensitized animals showed no gross signs of tuberculosis.

Allergic: In the allergic group one animal died during the fifth week, due to pneumococcus pneumonia. At the site of the virulent inoculation in the groin there was a small lymph node with caseous centre, but there was no evidence of dissemination of the tuberculosis. Two animals in this group were sacrificed for the sake of comparison in the twenty-first week. They showed a few tubercles in spleen and lung, but no extensive disease. Nine animals are alive and in good condition at the twenty-sixth week.

Comment: On the average the animals in this experimental series lived somewhat longer than those in the series already reported (11), the probable reason being the smaller dose of virulent tubercle bacilli (0.1 mgm. as compared with 0.4 mgm.). In general, however, the findings in the present series corroborate those in the series just mentioned. In both series the extensive involvement of the lungs of the desensitized pigs was noted, while the livers and spleens of the same animals showed no gross sign of tuberculosis. This was in contrast to the control animals which, after the fourth week, always showed miliary tubercles in lung, liver and spleen.

Another difference between the desensitized and the control group of

pigs should be recorded, namely, the great difference in number of acid-fast bacilli in the lungs of the animals. An impression-smear made from a cross section of the lung of any of the desensitized animals, with its extensive tuberculous pneumonia, will show large numbers of acid-fast bacilli in each oil-immersion field. An impression-smear made similarly from the lung of one of the control animals usually shows no acid-fast bacilli. Repeatedly we have dissected one of the miliary tubercles from the lung of a control guinea pig, teased the structure apart carefully and stained it, only to find no acid-fast microörganisms.

DISCUSSION

Experiments involving large numbers of desensitized guinea pigs enable one to predict with a considerable degree of certainty the pathological picture which will be found in animals of this type. During the initial stages of desensitization the animals lose weight and muscle tone, and many of them die from nonspecific pneumonia. If there is a high mortality amongst the allergic animals during desensitization it should be remembered that the remaining animals represent a select group, and due allowance must be made for that fact in constructing mortality curves.

In later phases of the experiment, death is due to tuberculous pneumonia which is frequently so extensive as to cause complete hepatization of the lungs. This pneumonic process becomes evident in normal-desensitized pigs during the third month after virulent infection and in allergic-desensitized animals during the fourth or fifth month. Acid-fast bacilli can be demonstrated in enormous numbers in smears from the lungs of these animals, whereas demonstrable bacilli are few or completely lacking in similar smears made from the lungs of allergic guinea pigs.

Fully as characteristic as the extensive tuberculous pneumonia found in the lung of the desensitized guinea pig is the relatively insignificant change in its spleen. The spleen remains practically normal in size, and shows no gross tubercles in spite of a large content of tubercle bacilli as demonstrated by bacteriological studies.

The curves shown in chart 1 indicate that, in comparison with the allergic animals, the allergic-desensitized animals had lost a considerable degree of the protection they had acquired from their primary infection. All of them were dead by the end of the sixth month while 45 per cent of the allergic animals similarly infected with virulent tubercle bacilli were still alive. Our most recent experiment shows three-fourths of the allergic

animals alive during the sixth month after virulent infection. The question of the relative merits of allergy and immunity needs further elucidation: what are all the factors which enter into the desensitization process that might undermine the immunity associated with first infection?

Immunity to tuberculosis is relative. Under ordinary experimental conditions it is nonexistent in the normal guinea pig inoculated with virulent tubercle bacilli. It operates adequately in allergic, previously infected animals where the dose is small; it delays and modifies the disease which follows large doses. The allergic animal may survive six months after virulent infection and show no sign of progressive disease but at twelve months may die with chronic ulcerative tuberculosis of the lungs. Similar but much shorter delay appears to occur in allergic-desensitized animals which may show no disease at eight or ten weeks after infection but will develop extensive tuberculous pneumonia and die before twenty-five weeks have elapsed. The interplay of these phenomena needs understanding and interpretation.

SUMMARY

1. Desensitized guinea pigs subjected to infection with virulent tubercle bacilli characteristically develop extensive tuberculous pneumonia.

2. The spleens of the same animals, though showing no gross tubercles, contain tubercle bacilli in large numbers.

3. Normal-desensitized guinea pigs (animals never permitted to become allergic) succumb to tuberculosis before even the normal control animals have died.

4. Mortality records kept over a period of many months indicate that, in comparison with allergic animals, allergic-desensitized guinea pigs have lost a considerable degree of the protection that follows a primary infection.

5. These observations indicate that it is unsafe on the basis of present knowledge to conclude that the phenomena of allergy are an unessential part of the mechanism of defense against tuberculosis.

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ACCESSORY STOMACH IN THE RIGHT THORAX

TOM LOWRY[1] AND LEWIS J. MOORMAN[1]

Baby B, the first born of healthy young parents, was delivered December 13, 1936, weight 6 pounds 6 ounces. The postnatal course was in every respect normal until the eighth day, when marked dyspnoea and cyanosis suddenly developed. Respiration was rapid and labored with decided limitation of expansion on the right. The temperature was normal. There was dulness over the right thorax posteriorly and a few fine râles were heard at the right base. It was impossible to determine the exact position of the heart, however thorough physical examination was considered inadvisable because respiratory catastrophy seemed imminent. Even the fluoroscopic examination was interrupted for the administration of oxygen and carbon dioxide.

An X-ray film made at this time was interpreted by Dr. John A. Heatley as follows: "Extreme atelectasis of the right lung. Same condition less marked left lung." (See figure 1.)

After administration of carbon dioxide and oxygen for a few hours, the X-ray film showed a clearing of the left lung with a very marked displacement of the mediastinal structures to the right. The following day physical signs and X-ray findings had not changed. It was necessary to continue the use of oxygen to prevent marked cyanosis. Normal saline and Hartman's solution were given daily subcutaneously, and feedings were continued by nasal catheter. Metrozol, caffein, and atropine were also employed.

After a period of ten days there was no change in the general condition and the clinical findings, including X-ray examinations, remained the same. Because of the stationary condition and the atelectasis of the right lung, artificial pneumothorax was attempted with the hope of relieving intrapleural negative pressure and thereby improving respiration. The manometer displayed no evidence of a free pleural space, and a brownish fluid escaped through the needle. Fifty cc. were withdrawn with marked improvement in the respiration and corresponding reduction in cyanosis. An X-ray film after removal of fluid showed what

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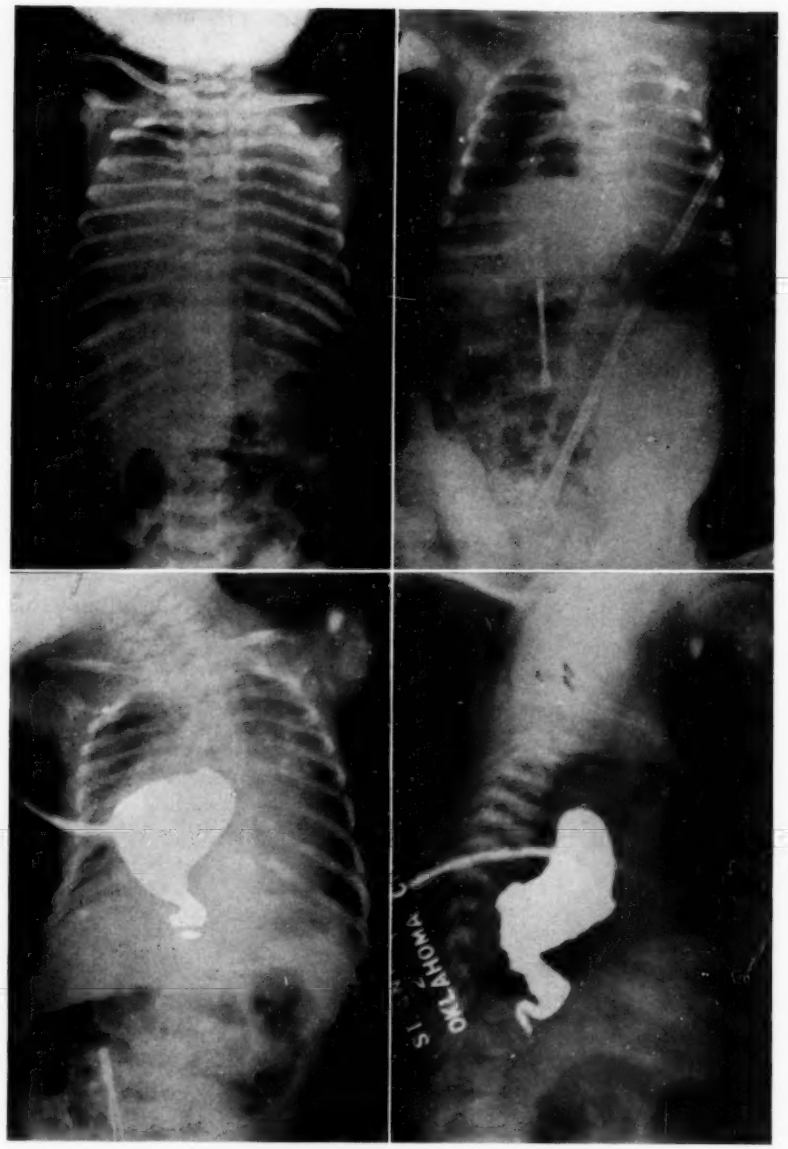

FIG. 1

FIG. 2

FIG. 3

FIG. 4

FIG. 1. Note uniform opacity, particularly throughout right lung.

FIG. 2. This film was made after the withdrawal of fluid. Note increased areation of the right lung and the presence of an opaque oval shadow with fluid level; also small accumulation of air above fluid level.

FIG. 3. This film was made after aspiration of fluid and the introduction of iodized oil. It is interesting to note what appears to be pylorus and caput with abortive attempt to reproduce duodenum.

FIG. 4. This film represents transverse view of fig. 3.

appeared to be a cyst or encapsulated fluid with an air bubble and a fluid level. (See figure 2.)

Aspiration was repeated every other day for ten days, after which the fluid became so thick and viscid that it was thought best to introduce a retention catheter. About 50 cc. of fluid was withdrawn through the catheter daily. Under this regimen, with proper intervals between aspirations, the child was comfortable, took regular feedings and maintained his weight.

The laboratory examinations of the fluid revealed no diagnostic or specific findings. In the hope of differentiating between a congenital cyst of the lung without bronchial communication and a mediastinal cyst, artificial pneumothorax was again attempted. However it was impossible to find the pleural space. The complete aspiration of fluid and the introduction of lipiodol, followed by posteroanterior and lateral X-ray films, suggested a cyst of mediastinal origin. (See figures 3 and 4.)

After several weeks of observation and the completion of the above diagnostic studies, surgical approach was considered and Dr. Horace Reed was consulted. In view of the good general condition at the time, and the danger of major intrathoracic surgery in an infant two and one-half months old, Doctor Reed advised against immediate surgery.

At this time, the films and a brief history were sent to Dr. Evarts A. Graham. After studying the X-ray films, Doctor Graham, on March 13, wrote as follows:

I am not certain by any means that the condition is one of a pulmonary cyst. I really have never seen anything quite like the condition presented. I would be a little more inclined, however, to think that the child has a tumor of the mediastinum rather than a cyst of the lung.

On April 1, the patient was sent to Doctor Graham for diagnostic study and surgical treatment if deemed advisable. The following quotation was taken from Doctor Graham's letter of April 13:

I had expected by this time to have operated on baby B, but unfortunately the youngster developed a cold which made it necessary to postpone the operation. In the meantime, we have come to the conclusion that this tumor has gastric mucous membrane in it. The contents contain all of the characteristic properties of gastric juice. It contains a considerable amount of hydrochloric acid and pepsin and one drop will coagulate three or four cc. of milk. We feel, therefore, that the tumor is either a teratoma containing gastric mucosa or it is an accessory stomach.

April 27, 1937, Doctor Graham reported the following:

I operated on the baby about ten days ago. I found a large tumor of the mediastinum which was so firmly attached to the superior vena cava and to other structures in the mediastinum that it was impossible to get it all out. I did, however, remove most of it and I felt that the remaining portion would probably undergo necrosis because of several transfixion sutures which I placed through the remaining portions. I felt that these sutures would cut off the blood supply. In spite of the fact that the operation was carried out under intratracheal anesthesia we had to stop twice because of respiratory difficulties. At the close of the operation, however, the baby seemed to be in excellent condition. We had already obtained some blood for transfusion and we, therefore, gave the blood to it. A few hours after the operation it suddenly stopped breathing and efforts at resuscitation were unsuccessful. An autopsy was performed. There was no apparent cause of death and the only abnormal finding was the remaining portion of the thoracic tumor which I have already stated I was unable to remove. There was a thin connection between the remaining portion of tumor and the esophagus which gave the impression that there had originally been a channel of communication through the connecting band. At the time of the autopsy, however, no communication could be demonstrated. The tumor itself was an accessory stomach which seemed in all respects to be practically normal. There was even an attempt to form a pylorus. The mucous membrane was exactly like that of a normal stomach as were also the submucosa and the muscle layers.

Before operation a number of studies were made on the digestive character of the secretion of the tumor. For example, it contained a large amount of free hydrochloric acid, apparently a normal amount of pepsin and a normal amount of rennin. One curious and interesting feature noticed was that feeding the baby into the normal stomach had no effect whatever in stimulating any increased amount of hydrochloric acid in the thoracic stomach. The secretion of hydrochloric acid from the thoracic stomach occurred in cycles of about twelve hours each. The maximum amount of hydrochloric acid was therefore reached about every twelve hours.

After looking at the autopsy specimen, I feel certain that we could not have removed all of the tumor without almost certainly tearing the vena cava. I still do not understand what caused the baby's death. There was no fluid to speak of or any trapped air in the thoracic cavity and the child had been getting inhalations of oxygen continuously since the operation. Evidently the operative procedure was just too much for the baby to stand. On the other hand, it probably could not have lived much longer without the operation because the secretion from the tumor was already beginning to digest the skin around the drainage opening. I believe that serious infection would have occurred sooner or later.

DISCUSSION

Early in the course of the case, the aspirated fluid, though varying in color and consistency, was at times of such a character as to suggest fluid from the normal stomach. However, attention was diverted from the stomach because X-ray studies indicated that the intrathoracic mass was definitely in the right thorax with diaphragm and liver normally situated above the stomach which exhibited the usual air bubble immediately beneath the dome of the left diaphragm.

With X-ray evidence of the normal position and relationship of the stomach and adjacent structures, the similarity of the aspirated fluid to stomach contents was disregarded; consequently tests for free hydrochloric acid and gastric ferments were not made until after the patient was referred to Doctor Graham.

Böss (1) presents a case of mediastinal cyst lined with typical gastric epithelium, in a child three years and nine months old. The preoperative diagnosis was infiltrating tumor with cavity formation extending from mediastinum into right thorax. Attempted surgical removal of the tumor proved fatal because of profuse haemoptysis. At autopsy a cyst was found between the right lower lobe of the lung and the vertebral column. Further examination revealed a perforating peptic ulcer opening into the lower lobe of the right lung. This was apparently the source of the fatal haemoptysis. The author calls attention to four other reported cases of mediastinal cysts containing gastric mucosa, but refers to his case as being the only one on record with lining entirely composed of gastric mucosa.

Ladd (2) reports 10 cases of duplication of the alimentary tract, all of which were in the abdomen. However, he states that the duplication may occur in the thorax. He also states that, so far as he knows, a correct preoperative diagnosis has never been made, but expresses the belief that with further experience, the condition might be suspected or diagnosed moderately often.

The authors desire to acknowledge the valuable diagnostic services of Drs. P. M. McNeill, Wm. Taylor and Ralph Bowen.

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ISOLATED HYPERPLASTIC ULCERATIVE TUBERCULOSIS OF THE SMALL INTESTINE[1]

SIDNEY E. WOLPAW[2]

Ulcerative tuberculosis of the intestinal tract occurring as a complication of pulmonary tuberculosis, and the hyperplastic tuberculosis of the ileocaecal region, are both well known clinically and have been frequently described in the literature. Much less well recognized, however, are those instances of tuberculosis, usually of the hyperplastic type, limited solely to the small intestine, and usually found in the absence of active parenchymal pulmonary disease. These isolated tuberculous lesions of the small intestine are not common; but three examples have been recorded in 9,100 autopsies at the Cook County Hospital from 1929 to 1936 inclusive, and but one in 40,800 surgical specimens during the same period. Nevertheless, the fact that they comprise a form of intestinal tuberculosis frequently amenable to successful surgical therapy makes them of considerable clinical importance.

A survey of the literature since 1900 (1) reveals at least twenty-six such cases of tuberculosis limited to the small intestine. In many instances, however, the pathological details are meagre so that some doubt exists concerning the exact nature of the lesion. In addition, the paucity of clinical, roentgenological and postmortem details concerning the presence of pulmonary or extrapulmonary tuberculous disease renders difficult any determination of the pathogenesis of the intestinal lesion, or any evaluation of the clinical course. Reference will be made, therefore, only to the more complete case reports in the literature and, in connection with the material which the author has had the opportunity of studying, the more important clinical and pathological aspects of the condition will be briefly reviewed.

CLINICAL ASPECTS

In general, patients with these tuberculous lesions of the small intestine fall into two major groups: a large group presenting a pro-

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longed chronic course, and a much smaller one presenting the features of an acute abdomen.

The chronic course: The classical picture produced by an isolated tuberculous lesion of the small intestine is that of a chronic, intermittent, intestinal obstruction which may vary in duration from a few months to as long as fifteen years. The disease occurs in both sexes and predominantly between the ages of twenty and forty (2 to 10).

Early in their course the patients present a wide variety of vague gastrointestinal complaints. Anorexia, nausea and vomiting, attacks of constipation, or alternating constipation and diarrhoea are common. These are accompanied by episodes of mild to severe abdominal pain, only occasionally related to the intake of food, and associated with abdominal distention and borborygmi. The early attacks may regress spontaneously, or with medication and diet, and there may then ensue periods of relative freedom from pain. In time, however, the attacks of abdominal distress increase in severity and the clinical evidence of a definite intestinal obstruction becomes pronounced. Weight loss, even to the point of emaciation, is common. Fever is usually absent or only slight in degree. Although occult blood is frequently found in the stool, gross haemorrhage is rare.

Examination of the patient generally reveals little of significance unless the signs of an advanced intestinal obstruction are present. In occasional patients palpable abdominal masses simulating neoplasms have been described, but this is distinctly unusual. Of particular diagnostic significance, as compared with the ordinary secondary ulcerative variety of intestinal tuberculosis, is the fact that the lungs on examination will almost always be found free of any active tuberculous disease. On roentgenological study, however, it is not uncommon to see apical fibrosis or the calcified remnants of an old primary complex either in the hilar area or the lung itself.

In the cases thus far recorded the X-ray examination of the gastrointestinal tract has been of singularly little assistance in formulating a specific diagnosis. Early in the course of the disease the evidence of intestinal obstruction may be minimal so that it is readily overlooked. Again, since the examination of the small intestine is not a routine procedure, small lesions may be missed, unless the attention of the clinician and the roentgenologist is specifically directed to this part of the intestinal tract (11). In a few instances in which the obstruction has been very chronic, however, it has been possible to visualize stenotic segments of the small intestine (7, 9).

The diagnosis of these tuberculous lesions of the small intestine is rarely made clinically. Because of the inability to discover a lesion adequate to explain the prolonged and often peculiar symptomatology, patients are usually treated medically over long periods of time under various diagnoses. Frequently, because of the persistent abdominal pain or evidence of intestinal obstruction, the patients are subjected to exploratory laparotomy, and the diagnosis is then established at the time of operation. It is true that these isolated tuberculous lesions of the intestine present no pathognomonic features. Nevertheless, if it be remembered that such lesions are an important cause of chronic, intermittent, intestinal obstruction in individuals between the ages of twenty and forty, and if greater attention is directed roentgenologically to the small intestine in obscure cases of abdominal pain and chronic obstruction, the diagnosis should be suspected clinically with greater frequency than heretofore. An example of the chronic course of the disease is illustrated by the following case.

Case 1: B. K., a thirty-two year old colored male, was admitted to the Cook County Hospital on May 6, 1934, because of an attack of abdominal pain of two days' duration. Beginning in January, 1933, he developed recurrent attacks of severe epigastric pain not related to food intake, and with radiation to the left flank and the left costovertebral region. These episodes were occasionally accompanied by constipation and distention but not by nausea or vomiting. The patient had anorexia and had lost nearly thirty pounds in weight during the year preceding his hospital admission. Twice during 1933 he had sought medical attention and had been hospitalized and studied for a possible peptic ulcer. However, gastrointestinal investigation with barium meal, barium enema, gastric analysis and proctoscopy had been entirely negative. A Sippy regimen had afforded a slight degree of relief.

Examination at the time of admission revealed little of importance. The patient did not appear acutely ill but showed evidence of considerable weight loss. His temperature was 100.4°F., pulse 76, respirations 26, and blood-pressure 108/64. The heart and lungs showed no abnormal findings. The abdomen was soft, but there was tenderness in the left upper quadrant. There were no palpable masses. The stools were negative for blood. The blood and spinal fluid Wassermann tests were negative. The white blood count was 7,700. Gastrointestinal examination with a barium meal and a barium enema failed to reveal any abnormality. A chest film showed the lungs to be clear. On cystoscopy the right ureteral orifice could not be identified and with intravenous pyelograms the right side failed to be visualized. The left kidney and ureter appeared normal.

The evidence seemed insufficient to ascribe his predominantly epigastric and left-sided pain to a genitourinary disease. No definite diagnosis could be established, however, and the patient was discharged by release to be observed in the outpatient department.

The patient was readmitted to the hospital on October 12, 1934, because of the persistence of his complaints. Again, examination was essentially negative except that 4 cm. below the xyphoid process there was palpated a small mass which was thought to be an epigastric hernia. Because of the long duration of the symptoms and the inability to reach any satisfactory diagnosis, exploratory laparotomy was thought to be justified.

At operation on October 13, 1934, (Dr. Schrager) the abdomen was explored. In the upper ileum there was found an indurated mass involving about 8 cm. of the intestine. This segment was markedly thickened and the lumen appeared narrowed. The remainder of the intestinal tract was explored and appeared normal. There were a few small, firm, mesenteric lymph nodes. Fourteen centimeters of the small intestine were resected and a side-to-side anastomosis was performed.

The patient's postoperative course was uneventful. Two weeks after operation he was fever free, without pain, and on a soft diet. He was discharged from the hospital on October 26, 1934.

Further course: The patient was readmitted to the hospital in January, 1935. Following his operation the patient's period of freedom from symptoms was of short duration. Several weeks before this final admission he developed distention with generalized abdominal pain. In addition, he had marked diarrhoea with four to ten watery stools a day. Further weight loss had occurred.

At this time the abdomen was distended and there was generalized tympany. There was marked resistance to palpation with rebound tenderness. Both lower extremities were oedematous. A chest film revealed a slight mottled infiltration in the right apex. The sputum showed no tubercle bacilli. It was thought that the patient now had a generalized tuberculous peritonitis. His condition gradually became worse and he expired May 27, 1935. Permission for autopsy was not obtained.

Pathological report (Dr. Nieman): The specimen consists of 14 cm. of the small intestine. In the central portion the entire wall is thickened and quite indurated, and the lumen of the intestine is constricted to a circumference of 1.5 cm. In this area of constriction the mucosa shows an extensive ulceration which encircles the entire lumen. The edges of this defect are undermined, the floor is roughened and granular. Attached to this segment of intestine is a one-centimeter lymph node which is firm, and on section is grayish-tan in color.

Microscopical appearance: A section of the intestinal wall at the edge of the

FIG. 2

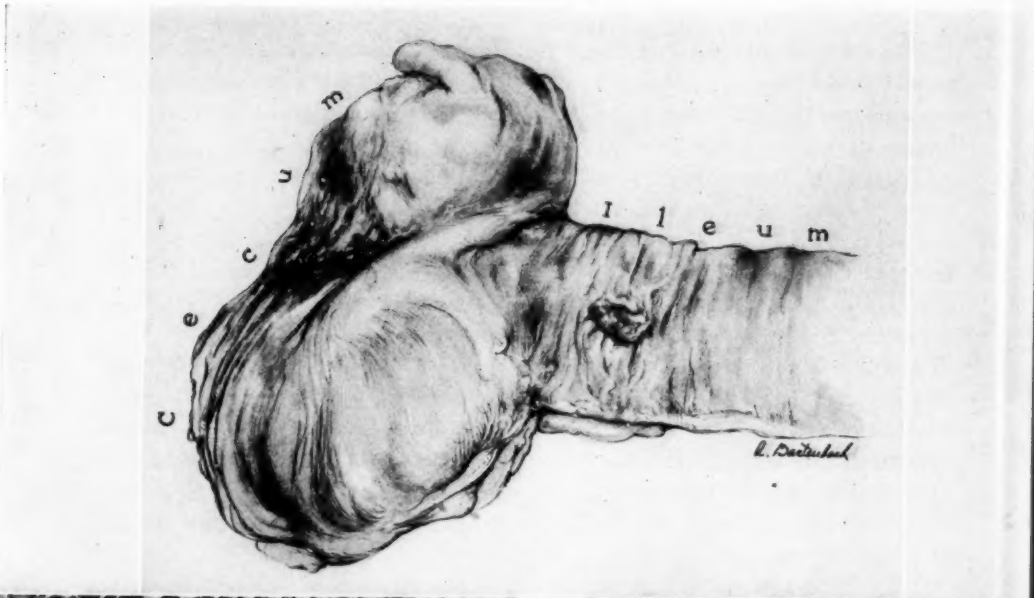

FIG. 1 FIG. 3

FIG. 1. Case 1. Section through the intestinal wall showing a portion of the thickened submucosa, the disruption of the *muscularis mucosae* by a large epithelioid cell tubercle, and the absence of necrosis. H. & E., × 60.

FIG. 2. Case 3. Isolated hyperplastic ulcerative tuberculosis of the terminal ileum.

FIG. 3. Case 3. Section through the floor of the ulcer showing a portion of the thickened submucosa. There is a dense tuberculous granulation tissue with numerous giant cells, indefinite tubercle formation, and a relative absence of necrosis. H. & E., × 60.

ulceration shows the mucosa to be thickened and heavily infiltrated with many lymphocytes and eosinophiles. The floor of the ulcer is composed of a dense granulation tissue, containing many lymphocytes, polymorphonuclear leucocytes and epithelioid cells. The submucosa is markedly increased in width and consists of a loose fibrous connective tissue infiltrated with lymphocytes and epithelioid cells. Scattered throughout the submucosa are many epithelioid cell tubercles of varying size, which frequently extend into and disrupt the *muscularis mucosae.* There are a few Langhans type giant cells and some of the tubercles contain small central areas of necrosis. The muscular layers are intact except that in scattered areas the muscle fibres are destroyed by the presence of small epithelioid cell tubercles. Similar tubercles are found in the serosa which is thickened and consists of a loose fibrous connective tissue (figure 1).

A section through the lymph node shows the architecture to be altered by the presence of numerous tubercles of varying size. The majority of these tubercles are composed of epithelioid cells. Giant cells are common. Only an occasional tubercle shows extensive caseation necrosis.

The clinical features of the majority of these lesions of the small intestine are thus well characterized in this patient. The prolonged history of abdominal pain with symptoms of mild intestinal obstruction, the failure of clinical and roentgenological procedures to clarify the diagnosis, the absence of active pulmonary tuberculosis, and the establishing of the diagnosis by exploratory operation are typical. Whether the late development of the tuberculous peritonitis is to be ascribed to dissemination of microörganisms at the time of operation, or whether the peritonitis and recent pulmonary lesion resulted from a dissemination from some other tuberculous focus in the body, must remain uncertain without postmortem examination.

The acute course: In a small group of patients the clinical course differs from the one previously described in that the history and physical examination suggest the presence of an acute surgical condition of the abdomen. This may take several forms. In a few instances, the rapid onset of abdominal pain, especially in the right lower quadrant, with nausea and vomiting, has led to the diagnosis of acute appendicitis. The true nature of the lesion is then discovered at operation; or, more commonly, the appendix is removed and the symptoms fail to be alleviated. The correct diagnosis is then revealed when further exploratory operative procedures become necessary because of the persistent abdominal pain or the onset of an acute intestinal obstruction (10, 12, 13).

In other patients with an acute onset the clinical picture is that of a perforated viscus with a localized or generalized peritonitis. At operation it is found that this results from the perforation of the tuberculous lesion which previously had been quiescent. This complication occurs much less frequently than in the secondary ulcerative form of intestinal tuberculosis (14, 15, 16).

Again, in certain patients who have been in apparent good health or who have had only minor gastrointestinal complaints, the onset of symptoms is with the picture of an acute intestinal obstruction (17).

Case 2: A. B., a sixty-nine year old white female, was admitted to the Cook County Hospital on November 11, 1936. She was in good health and able to work until six weeks before her admission to the hospital. At that time she noted slight colicky abdominal pain in the region of the umbilicus with the passage of several tarry stools. Two weeks before her admission the patient suddenly developed severe and prolonged abdominal cramps with marked distention and nausea. Hospitalization was advised and refused. With enemas, medication, and a liquid diet the symptoms subsided to a certain extent. However, she remained weak, developed a temperature to 101°F. and lost about twenty pounds in weight. In addition, there developed scaling of the skin of the face and body with some pruritus. The past history was essentially negative except for prolonged constipation and a long standing pyelitis and cystitis for which treatment had been carried out in another clinic.

On examination her temperature was 99°F. and blood-pressure 154/78. The skin of the face and body was red and scaling. The heart and lungs were negative. The abdomen was distended, especially in the flanks, and there was active peristalsis. There was no tenderness, and no palpable masses except the liver which was four finger breadths below the costal margin.

Laboratory examination showed the urine to contain much albumin and many pus cells. The white blood count was 7,400. The blood urea nitrogen was 16 mgm. in 100 cc. The blood Wassermann was negative. The stools contained blood.

The patient was too ill for thorough gastrointestinal studies, but a barium meal with the patient in the horizontal position revealed no abnormality of the stomach or duodenum. Barium enema showed normal conditions.

The patient had a low grade daily temperature elevation to 99° or 100°F. Her major complaints were referable to the exfoliative dermatitis. The abdomen remained distended. There was occasional abdominal distress, with the passage of small clots of blood. Her condition was too poor to warrant further investigative work or operative procedures. She expired December 16,

1936, five weeks after admission to the hospital. Four days before death her temperature rose to 103°F. and râles were heard at both lung bases.

Autopsy (Dr. Kirshbaum): The autopsy was performed shortly after death. Only the relevant features will be presented. The body was that of an emaciated, senile, white female. The abdominal cavity revealed the liver to be 8 cm. below the xyphoid process and 7 cm. below the right costal margin. The intestinal loops were distended with gas. Several loops of the jejunum were matted together by dense fibrous adhesions. Between the pleura and the diaphragm at the right base were small plaques of calcified material. Lungs: The left lung was moderately distended and crepitant throughout. On section the upper lobe was dry and the lower lobe light purplish-gray and moist. The right lung showed the pleura to be covered with firm fibrous tags. On section the lung was subcrepitant, moist, and deep purplish-red with darker purplish-red granular areas in the lower lobe. In the apex of the upper lobe the lung was indurated and dark purplish-gray. The bronchi were slightly dilated. The middle lobe contained a firm granular area 6 x 4 x 3 cm. and was studded with smaller light purplish-gray areas. Spleen weighed 120 grams. Liver weighed 1,590 grams. Small intestine: The mucosa was light yellowish-green to purplish-gray. In the lower jejunum, where several intestinal loops were adherent, the wall in an area 2.5 cm. long was indurated and thickened to a width of 6 mm. The lumen of the intestine in this area was slightly constricted. The mucosa in this region presented an ulceration 4 x 2.5 cm. The floor of the ulcer was purplish-tan and firm. In its centre was a 10 mm. opening which led into a 4 x 3 cm. cavity in the mesentery. The serosa of the jejunum in this area was thickened, injected, and light purplish-gray. The mesenteric lymph nodes about the cavity formed a 10 x 4 x 3 cm. mass. On section the nodes varied from 8 to 35 mm. in diameter. They were light purplish-gray mottled with areas of yellowish-gray. The remainder of the small and large intestines presented no abnormalities.

Microscopical appearance: Ulcer of jejunum: The ulcer extends deeply into the submucosa and its floor is composed of a layer of necrotic tissue. The submucosa itself is thickened and consists of a moderately dense, cellular granulation tissue. The cellular infiltration consists of lymphocytes and epithelioid cells. The muscular layer is frequently disrupted by an infiltration of similar cells. The serosa is thickened and likewise contains many lymphocytes and epithelioid cells. A few small blood vessels near the ulcer are filled with thrombi rich in fibrin. No tubercle bacilli are demonstrable with Ziehl-Neelsen stains. Mesenteric lymph node: The structure of the lymph node is replaced by tubercles of varying size containing extensive areas of caseation necrosis. The tubercles are bordered by a dense connective tissue, although

in scattered areas this connective tissue is quite cellular and infiltrated with many lymphocytes. Right upper lobe: The alveolar structure of the lung is obliterated by extensive areas of fibrosis containing deposits of anthracotic pigment. Scattered throughout this fibrous tissue are numerous small collections of lymphocytes. The alveoli in areas adjacent to the fibrosis are distended, free of cellular exudate, and their walls are thickened.

Final anatomical diagnosis: Tuberculosis of the jejunum and the regional lymph nodes, indurative tuberculosis of the apex of the right upper lobe, fibrous obliteration of the right pleural cavity with calcified plaques at the base of the lower lobe, confluent bronchopneumonia of the right middle and lower pulmonary lobes, passive congestion of the liver and spleen, cloudy swelling of the kidneys, parenchymatous degeneration of the myocardium, atherosclerosis of the aorta, emaciation.

Finally, isolated tuberculous lesions of the small intestine may be discovered incidentally at autopsy in individuals who have had no apparent gastrointestinal symptomatology.

Case 3: The patient was a seventy-six year old white female who was admitted to the Grant Hospital on December 25, 1936. She had been in good health until the spring of 1936 at which time she noticed some loss of weight. There were no complaints of pain, cough, dyspnoea, and there were no gastrointestinal disturbances. About two months before her hospital admission her abdomen increased in size, her legs became oedematous, and cough and orthopnoea appeared. On examination the patient showed evidence of weight loss. The lower extremities were oedematous. The left chest was flat as high as the third dorsal vertebra, and the dulness extended into the axilla. The breath-sounds were audible but not as intense as on the right. The right lung was resonant and the breath-sounds distinct. A few râles were heard at both lung bases. The left cardiac border was 5 cm. to the left of the midsternal line. The tones were distinct and there were no murmurs. The abdomen was markedly distended and flat. Shifting dulness was present. The haemoglobin was 70 per cent, the white blood count 5,000, red blood count 4,800,000. The differential showed 58 per cent neutrophiles, 40 per cent lymphocytes, and 2 per cent mononuclear cells. Thoracocentesis in the posterior axillary line secured 1,500 cc. of straw colored fluid with a specific gravity of 1.014. Smears showed numerous lymphocytes and a few polymorphonuclear leucocytes. There were no tubercle bacilli.

The patient's course was downhill. Her respirations were 40, pulse 120, and temperature 99°F. She expired twelve hours after admission to the hospital.

Autopsy: The body was that of a poorly nourished and poorly developed white female. The abdomen was markedly distended. The abdominal cavity contained about ten liters of a slightly cloudy fluid. The peritoneal

surfaces were studded with pin-head sized pearly white nodules. The left pleural cavity contained 1,000 cc. and the right 500 cc. of a clear straw colored fluid. The parietal and visceral pleura contained many pin-head sized white nodules. The pericardial sac was free. Lungs: Both lungs were crepitant throughout. On section considerable frothy fluid escaped from the bronchi. There were no areas of consolidation. In the left hilum area there was a large partially calcified, caseous and anthracotic peribronchial lymph node. The heart weighed 350 grams, the spleen 695 grams and the liver 1,500 grams. The kidneys weighed 248 grams; the capsule stripped with slight difficulty leaving a slightly granular surface. Intestine: Four centimetres above the ileocaecal valve in the ileum the intestinal wall was firm and thickened over about one-third of its circumference. This area measured 2.5 cm. in length. The intestinal wall in this area was 5 mm. in thickness. The mucosa was ulcerated, the edges of the ulcer being raised and indurated. The base of the ulcer was firm. The serosa was thickened and contained numerous pin-head sized nodules (figure 2). The remainder of the intestines presented no abnormalities.

Microscopical appearance: The mucosa at the edge of the ileal ulcer is thickened by a round-cell infiltration and the presence of numerous tubercles. The ulcer extends nearly to the muscular layer and its floor consists of a moderately dense granulation tissue with many tubercles having small necrotic centres. The submucosa is markedly thickened and composed of a fairly dense connective tissue. Throughout the submucosa are many epithelioid cell tubercles with Langhans type giant cells and occasional small necrotic centres. The muscular layer is likewise thickened, frequently interrupted by small tubercles, while the individual muscle fibres are disrupted by a round-cell infiltration. The serosa is thickened and contains several poorly defined tubercles (figure 3). Ziehl-Neelsen stain reveals the presence of occasional acid-fast bacilli. Mesenteric lymph node: The structure of the lymph node is intact except for the presence of scattered tubercles with small necrotic centres. Langhans type giant cells are frequent. Spleen: The normal architecture of the spleen is destroyed by diffusely scattered tubercles in various stages of development. A few have caseated centres. Others have central Langhans giant cells while others consist for the most part of epithelioid cells.

Final anatomic diagnosis: Isolated hyperplastic tuberculous ulcer of the ileum, tuberculous peritonitis and pleuritis, chronic hyperplasia of the spleen with miliary tubercles, slight periportal fibrosis of the liver, arteriosclerosis of the kidneys, slight hypertrophy of the heart, oedema of the legs.

DISCUSSION

Pathological aspects: In their pathological details these tuberculous lesions of the small intestine present rather uniform findings which adequately explain the clinical aspects previously described.

Except for their rare occurrence in the duodenum (6) little can be said from the small number of reported cases concerning any site of predilection of these lesions. They have been described with about equal frequency in the lower jejunum, and the upper and lower portions of the ileum. Of particular significance in determining the feasibility of surgical interference is the fact that the lesions, as in the cases presented, are frequently single. Nevertheless, because multiple areas of involvement have been described (6, 12, 3) the importance of exploring the entire extent of the small intestine is apparent. The length of intestine involved is variable. Most commonly the diseased portions are under 15 cm. but lengths as great as 25 cm. have occurred (4).

In this variety of intestinal tuberculosis the outstanding gross feature is the marked thickening and induration of the intestinal wall, which from peritoneum to mucosa may be as great as 2 cm. in extent. Although the process may involve only a portion of the wall as in case 3, it is usually annular so that there is produced intestinal masses simulating neoplastic growths. The thickening of the intestinal wall is the result of an extensive connective tissue proliferation in all the layers, without the marked necrosis and caseation which characterizes the enterocolitis complicating pulmonary tuberculosis.

The constant and most striking characteristic of these lesions is the narrowing of the intestinal lumen from a slight degree as in case 3 to the nearly complete stenosis as in the case of Masson and McIndoe (5). The narrowing is brought about primarily by the thickening of the coats of the intestinal wall with consequent encroachment upon the lumen, and to a lesser extent by the constriction of the connective tissue in the wall. It is to this characteristic of hyperplastic tuberculosis of the small intestine that the major symptoms of pain and obstruction can be readily attributed. As an added factor the frequent occurrence of firm adhesions in the region of the involved bowel, with distortion of the intestinal canal, may also play a part in the production of the obstruction. In case 2, for example, it appeared that the extensive intestinal adhesions were as much responsible for the symptomatology as the partial constriction of the lumen by the thickened wall. It is certain, however, that the major symptoms of pain and obstruction represent the end stages of the disease, which in its really early phases must be asymptomatic or subclinical in its manifestations. From the thickness of the intestinal wall in the reported cases, particularly those with a fairly acute onset, it is apparent that the process must have been

of long duration, antedating by considerable periods of time the clinical evidence of its presence.

Grossly, the intestinal mucosa in the diseased area is thickened and shows some degree of ulceration. In exceptional instances, however, the thickening may be sufficiently great so that the mucosa is thrown into folds and presents a polypoid appearance (5). The ulcerations rarely extend beyond the submucosa. It can readily be understood, therefore, why perforation is uncommon. Even should the ulcerations extend deeply the slowness of the process permits the formation of adhesions which will restrict the peritonitis to a local one when perforation does occur. The serosa, likewise, is increased in width and presents on the surface tubercles arranged along the lymphatics. The latter are of diagnostic value at the time of operation in distinguishing the lesion from carcinoma.

Although enlarged mesenteric lymph nodes are a constant finding the presence of extensive caseation is uncommon. The nodes are generally one centimetre or less, hyperplastic, with small areas of conglomerate tubercles. Calcification of the mesenteric nodes is apparently a rare occurrence (5), although since roentgenological studies have not been carried out small areas of calcification might readily have been missed.

Microscopically, these lesions are characteristic of a proliferative tuberculous process in that there is found an abundant tuberculous granulation tissue with extensive round-cell and epithelioid cell infiltration; and epithelioid cell tubercles with but a moderate amount of caseation necrosis.

It is seen that in the nonulcerated areas the thickening of the mucous membrane results from a rich cellular infiltration of lymphocytes, plasma cells, eosinophiles, and occasional tubercles. This infiltration may be sufficiently marked to produce the polypoid appearance previously mentioned. The *muscularis mucosae* usually remains intact unless the ulceration is deep.

Microscopically, it is the involvement of the submucosa which accounts for the major thickening of the wall. The picture may vary. Frequently the submucosa consists of a fairly dense connective tissue with few or no tubercles but with a round-cell and epithelioid cell infiltration. Giant cells and necrosis may be scanty or absent. On the other hand the submucosa may be increased in width by the presence of a large number of tubercles with many giant cells. The tubercles are for the most part epithelioid in type with minimal central necrosis.

There is generally hypertrophy of the muscular coat. It remains intact unless there occurs very deep ulceration or a disruption of muscle fibres by scattered tubercles or a cellular infiltration. The serosa shows a connective tissue proliferation and generally contains numerous tubercles.

Because of the predominantly proliferative character of the process tubercle bacilli are not readily demonstrable in the lesion. The microscopical picture in the majority of instances, however, is sufficiently characteristic to establish the diagnosis. The paucity of tubercle bacilli in the lesion, of course, explains the failure, as a diagnostic procedure, of stool examination for the microörganisms.

Pathogenesis: Although the clinical and pathological features of this form of intestinal tuberculosis are well understood, the pathogenesis of the condition, to a considerable degree, remains obscure. Indeed, in the majority of the reports in the literature and even in the more comprehensive works on tuberculosis this subject receives scant attention. Although it is beyond the scope of this paper to enter into the controversial issues concerning the pathogenesis of intestinal tuberculosis, certain facts with respect to hyperplastic tuberculosis of the small intestine are worthy of consideration.

The failure to recognize that the pathogenesis of this lesion varies in different instances explains, in part, some of the confusion in the literature on this point. In addition, conclusions which have been reached from purely clinical rather than from postmortem studies are open to question, since it is well known that examination alone may fail to reveal pathologically important, although clinically insignificant, tuberculous foci. Finally, it is true that even autoptic examination may occasionally fail to clarify the pathogenesis of a given lesion.

By many authors hyperplastic tuberculosis of the small intestine is considered to represent a primary intestinal infection. The major argument in support of this contention is that these lesions are seldom accompanied by evidence of other tuberculous foci in the body. However, in reviewing the cases reported in the literature there is no satisfactory example of hyperplastic tuberculosis of the small intestine which can be incontrovertibly considered as a primary intestinal infection. The opinions which have been based solely on clinical grounds without autopsy confirmation (9, 10, 18) cannot, of course, be relied upon. As illustrated in cases 2 and 3, if careful postmortem study is performed, there will be frequently found older tuberculous lesions elsewhere in the body particularly in the lungs and the thoracic lymph nodes.

Only in the case of Cornils (14) is attention drawn to the fact that the only tuberculous lesion found in the body was that of the intestine. Nevertheless, according to modern concepts, the absence of tuberculosis in the mesenteric lymph nodes speaks strongly against a primary tuberculous infection. If tuberculosis is present in the mesenteric lymph nodes, it is seldom of the caseous character as would be expected in a primary infection. Calcification, which occurs frequently in primary infections, is also a rare occurrence in the lymph nodes accompanying hyperplastic lesions of the small intestine.

Of significance, too, is the reported age incidence of this form of intestinal tuberculosis. It occurs almost exclusively in adults and rarely below the age of twenty (2). Primary intestinal infection, on the other hand, is found predominantly in children. It would be expected, therefore, that hyperplastic tuberculosis of the small intestine should be found more commonly in the younger age groups. Studies on primary intestinal infection (19, 20, 21), however, do not indicate any unusual incidence of this type of lesion in children.

It may be concluded, therefore, that although hyperplastic tuberculosis of the small intestine may represent a primary intestinal infection, its occurrence as such must be rare and can be proved only by careful postmortem examination.

The majority of authors regard these lesions of the small intestine as reinfections resulting from the ingestion of tubercle bacilli either from sputum or food, particularly milk and meat.

In most instances, however, sputum can be eliminated as a major source of infection since it has already been emphasized that hyperplastic tuberculosis of the small intestine seldom occurs in the presence of active pulmonary disease. This was true of the three cases previously presented. The suggestion has been advanced, too, that the tuberculous lesion of the intestine is a complication of a previously active pulmonary focus which upon healing still leaves behind it the slowly progressive intestinal disease. This explanation has been utilized particularly in those instances such as case 2 in which old indurated apical disease has been found. It may well be that such an explanation accounts for individual examples of this type, but it cannot be utilized for those cases in which no preëxisting disease has been demonstrated.

A more likely possibility is that infection may occur through the ingestion of contaminated milk and food. This explanation has been offered particularly in the cases in which the tuberculous lesion has oc-

curred in the lower ileum where stagnation of the intestinal contents is known to take place. Unlike the common localization of the secondary ulcerative variety of tuberculosis in this area, it has already been pointed out that isolated hyperplastic tuberculous lesions have no predilection for any particular portion of the small intestine. Furthermore, the widespread use of pasteurization of milk and the inspection of cattle has removed the major factors of digestive tract infection. Even in countries where pasteurization of milk and food inspection are not generally carried out, hyperplastic tuberculosis of the small intestine is an uncommon finding.

Infection through the digestive tract must therefore be considered as a distinct, though not common, possibility in explaining the pathogenesis of many cases of hyperplastic tuberculosis of the small intestine. Since a history of this type of infection is difficult to obtain, however, this factor can be proved only with considerable difficulty.

From the evidence available in the more thoroughly studied examples of this form of intestinal tuberculosis, it appears that the pathogenesis of many cases is most satisfactorily explained by considering them as the result of a haematogenous dissemination of tubercle bacilli. The strongest evidence supporting this contention is the very frequent association of the intestinal lesions with other tuberculous foci in the body from which such a haematogenous dissemination could occur. Such foci have been found in the cervical lymph nodes, the thoracic lymph nodes, and older apical pulmonary lesions.

In this respect hyperplastic tuberculosis of the small intestine may be considered as an example of chronic isolated organ tuberculosis (22). It becomes analogous, therefore, to the tuberculosis of other parts of the body, notably the brain, kidneys, joints, adrenals, and lower urogenital tract which is to-day generally accepted as being haematogenous in origin. Pathologically, all of them represent isolated tuberculosis of a single organ, occurring in the absence of active pulmonary tuberculosis, associated with other preëxisting tuberculous foci, and presenting a chronic, slowly progressive clinical course.

Case 3 offers evidence in support of this pathogenesis of the intestinal lesion. Neither the patient's advanced age (seventy-six years) nor the anatomical findings indicated a primary intestinal infection. Reinfection through the digestive tract, while not capable of being absolutely disproved, was unlikely since the patient was a city resident and thus not likely to be exposed to contaminated milk or food; nor was there

evidence of a preëxisting active pulmonary lesion. Autopsy did reveal, however, a caseous thoracic lymph node of some age since partial calcification was present. It is probable that a previous haematogenous dissemination from this focus resulted in the localization of microorganisms in the lower ileum with the consequent production of a clinically latent isolated hyperplastic tuberculosis. That such a haematogenous dissemination could take place in this individual is illustrated by the final clinical course. From the caseous thoracic focus there occurred a dissemination of tubercle bacilli with the recent development of the tuberculosis of the peritoneum, pleura and spleen which resulted in the death of the patient.

Treatment: Those who have had experience with this type of intestinal tuberculosis are generally agreed that there is little to be gained from medical therapy. The isolated character of the lesion without significant pulmonary tuberculosis, the obstructive nature of the disease in its chronic course and the occasional occurrence of complications resulting in an acute condition of the abdomen make the treatment preëminently surgical. Both intestinal resection (2, 5, 10, 12, 16, 17) and entero-anastomosis around the involved area without resection (4, 6, 8, 13) have been successfully performed. The choice between the two procedures can be made, of course, only at the time of operation. It is dependent upon the general condition of the patient, the extent of intestine involved, the presence of intestinal adhesions, the presence of a perforated lesion with local or generalized peritonitis, and the presence of other known tuberculous foci in the body. If possible, the majority of surgeons express a preference for intestinal resection, since the eradication of such an isolated tuberculous lesion appears to offer a sounder basis for a complete and lasting cure.

SUMMARY

Three cases of isolated hyperplastic ulcerative tuberculosis of the small intestine are presented and the significant clinical and pathological aspects of the condition are reviewed.

The necessity of careful investigation of the small intestine in cases of obscure abdominal pain and prolonged intestinal obstruction is emphasized, since this entity is an important cause of chronic intermittent intestinal obstruction in patients between the ages of twenty and forty.

It is pointed out that the pathogenesis of the lesion is often obscure. In certain instances infection may take place through the digestive

tract although rarely as a primary intestinal infection. Postmortem evidence indicates that many of the lesions represent examples of isolated organ tuberculosis resulting from the haematogenous dissemination of tubercle bacilli.

The treatment of this form of intestinal tuberculosis is preferably surgical rather than medical. Successful results have been reported with both intestinal resection and entero-anastomosis about the diseased area without resection.

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INFLUENCE OF SULPHOCYANATES ON TUBERCULOSIS[1]

A Study of Sulphocyanates in the Hypertensive Tuberculous Patient, the Tuberculous Guinea Pig and in Media

JOHN STEIDL, WILLIAM STEENKEN, JR. AND FRED H. HEISE

In 1857 Claude Bernard (1) studied the toxic effect of sulphocyanates and concluded that they act as a muscle poison abolishing muscular activity. Pauli (2) in 1903 noted decrease in blood-pressure during the administration of cyanates for tabes, heart disease and neurasthenia. Since then a considerable literature has accumulated dealing with the use of sulphocyanates in hypertension. Many workers have been impressed by the useful hypotensive effect; among them are Goldring and Chasis (3), Schreiber (4), Gager (5), Bolotin (6), Maguire (7), Westphal (8), Palmer, Silver and White (9), Nichols (10), and Fineberg (11). Those who have been disappointed in the therapeutic effect, or who lay stress on the toxic manifestations include Egloff, Hoyt and O'Hare (12), Ayman (13), Weis and Ruedemann (14), Palmer and Sprague (15), Meakins and Scriver (16), and Logefeil (17).

In 1936 Barker approached the difficult problem of dosage from the point of view of the blood level of the sulphocyanates (18, 19). He found that the optimum therapeutic level in the blood was 8 to 12 mgm. per 100 cc., and that significant toxicity for adults began to appear at from 15 to 30 mgm. This new method of avoiding or controlling the more toxic manifestations of the drug may very well revive the use of sulphocyanates in the treatment of hypertension.

We have been unable to find any reference in the literature to the effect of sulphocyanate on the tuberculous patient with hypertension, and therefore report here the experience with three such patients, in addition to experimental data bearing on the subject.

Case 1:[2] A white physician of 36 had a family history of cardio-vascular disease. His father died at 52 during a cerebral episode; one brother died of

[1] From the Trudeau Sanatorium, Trudeau, New York.

[2] We are indebted to Dr. Warriner Woodruff of Saranac Lake for permission to report this case.

malignant hypertension at 37; his mother had a severe menopausal hypertension which persisted, and although still living at 71 has clinical and electrocardiographic evidence of myocardial damage. At the age of 23 the patient developed a tuberculous pneumonia, for which he rested a year and a half with good clinical results but without closure of cavity. At 25 he again relapsed with severe symptoms of toxaemia and a pneumonic process. At the end of a year, because of persistent symptoms, positive sputum and extensive involvement confined mostly to one side, a thoracoplasty was done on the right. Within a year he was rehabilitated and has remained well since. At the age of 29 the patient had his blood-pressure checked annually for a few years, but failing to find high pressures discontinued this practice, so that at the age of 36 his pressures were almost accidentally found to be 250/150. In the light of this information, headaches which had been attributed to severe migraine during the preceding six months, and haemoptysis six months previously which had been attributed to pulmonary tuberculosis, were now explained as due to the marked hypertension.

Potassium thiocyanate administered according to the method of Barker (18) resulted, at a blood level of 10 mgm. per 100 cc., in a reduction in pressure to 190/130–140. There was much relief of symptoms; particularly gratifying was the almost complete relief from headaches and a very marked sedative effect. Nevertheless, mild nocturnal "cardiac asthma" developed. While on vacation for a month he dropped the dose of sulphocyanate to one-half the required level to avoid any possible overdose, and the cardiac symptoms increased. Digitalis helped these symptoms, but an acute streptococcic sore throat at this time was an unfortunate complication. When he returned to work the blood level of sulphocyanate was found to be 3 mgm. per 100 cc. The following day he developed acute pulmonary oedema. When this cleared up there were some anginal symptoms. At the end of two months, following an improvement in his clinical condition, he was referred to Dr. Max Peet for sympathectomy and splanchnicotomy, which reduced his pressures from 260/150 to 170/110, at which level he is comfortable and able to work.

Case 2: A Swedish cook of 48, whose mother died of a "stroke" at 79, and whose maternal aunt at 76 has "kidney trouble," had a known hypertension of 250/150 for at least 10 years, with moderate dyspnoea on exertion. The onset of her tuberculosis was manifested by catarrhal symptoms, and the diagnosis was confirmed by positive sputum, X-ray of the chest, and physical signs. On admission to Trudeau Sanatorium on July 9, 1932, she was found to have a moderately advanced fibrotic tuberculosis confined to the right lung. This disease did not subsequently advance while under observation, but she did have occasional small haemoptyses and a constantly positive sputum. On July 15, 1933, she had a mesenteric thrombosis, from which she made a com-

plete recovery. Her blood-pressure was taken many times during residence, and varied from 200/130 to 254/165. The urine remained clear. The fundi showed arteriovenous nicking but no exudates. The heart was moderately enlarged, with accentuation of A2. A gastric ulcer developed, with haematemesis early in 1936, and was successfully treated with a Sippy diet. During the summer of 1936 she began to develop transient cerebral episodes, characterized by disorientation and confusion, urinary incontinence and some spasticity; within a few days these attacks would clear up without residual findings. Because of this alarming change in her symptoms it was decided to try her on sulphocyanate therapy according to Barker's method. A reëxamination at this time showed no change in the findings of the heart, eyes and kidneys. N.P.N. was 27 mgm. Average blood-pressure was 240/140. She received sulphocyanates from October, 1936 to the time of her discharge, April 30, 1937, with a reduction of blood-pressure to an average of 190/128, although the systolic did fall as low as 176 and the diastolic to 112 on occasions. Blood sulphocyanate varied from 8.2 to 15.2 mgm. per 100 cc. She still suffered an occasional cerebral episode, although there was a reduction in the frequency and severity. She complained of some weakness, which might be attributed to the treatment.

Case 3: A single white draftsman of 33 entered the Sanatorium on March 6, 1936, with a history of hypertension and marked renal changes of five years' duration. He stated that his pressures had been running about 140/130. Urine reports from his doctor showed the presence of albumen, red cells, and casts for a period of five years. On admission he was found to have a moderately advanced, active, exudative lesion confined to the lower three-fourths of the right lung. At this time his pressures were 160/90, but this relatively low pressure was thought to be due to the fact that he was acutely ill, with temperature to 101.4°F. He was also found to have intestinal tuberculosis. The urine showed albumen (2 gm. per litre on several examinations), many hyaline casts, many fine and course granular casts, a few pus cells and a few red cells. The apex beat was forcible, A2 accentuated, and there was a slight systolic apical murmur. The electrocardiogram showed a slight notching and slurring of the QRS complex in lead 1 and left axis deviation. The fundi showed arteriovenous nicking, but were free from exudates. N.P.N. was 35 mgm. On a very dry diet he was able to concentrate urine only to a specific gravity of 1016.

Because of the acute exudative lesion in the lung, the presence of intestinal tuberculosis and positive sputum (Gaffky X) pneumothorax was instituted. His tuberculosis was brought under control in a satisfactory manner, and his blood-pressure then rose to the old levels. He proved to be a bitter, complaining, refractory patient and found it difficult to understand why he could not

be promptly cured of his hypertension. Headaches, nervousness, insomnia, nausea, and abdominal uneasiness disturbed him a great deal. In spite of the fact that this is the type of case which is apt to give trouble due to poor clearance of sulphocyanate it was decided in August to try him on this drug, according to Barker's method. His blood-pressure ranged from 208 to 245 systolic and 94 to 136 diastolic, averaging 220/131 before treatment. He received the drug for only 36 days, and an effective concentration in the bloodstream only for two weeks. At the end of this time it was discontinued because he complained so bitterly of nausea; it is difficult to be sure how much of the nausea was due to the drug and how much was due to intestinal tuberculosis, which was producing a good deal of nausea before treatment was started. The blood concentration of potassium sulphocyanate never rose over 8.5 mgm. per 100 cc. In spite of this brief period of treatment his systolic pressure fell as low as 174 and his diastolic as low as 98 (on several occasions). The average blood-pressure during the nine days before treatment was terminated was 175/106. After treatment was discontinued the pressure rose gradually to 224/120. The tuberculosis did well during treatment with sulphocyanate and continued to do well nearly a year later.

The above findings tend to show that when sulphocyanate was fed to humans having hypertension complicated by tuberculosis the tuberculosis was not affected by the sulphocyanate.

EXPERIMENTAL

In order to prove experimentally whether sulphocyanate had an effect upon the disease tuberculosis or the tubercle bacillus, it was decided to run several experiments, one to observe the effect of various concentrations of sulphocyanate when added to solid media of known constitution upon the growth and virulence of human tubercle bacilli H37 Rv (20); the other to note the action of the sulphocyanate upon tuberculosis in the animal body (guinea pig) in which the route of infection and dosage was controlled.

Cultural experiment: Hohn's media was prepared and divided into four 150 cc. portions, each portion being enough to make fifteen slants of 10 cc. each. To one portion 11.5 mgm. of sulphocyanate, equivalent to .76 mgm. per tube, was added, to the second 22.5 mgm. or 1.52 mgm. per tube, and to the third portion 46 mgm. or 3.04 mgm. per tube was added. The fourth batch was tubed in 10 cc. portions and used as controls.

A suspension of the H37 Rv organisms was then prepared by triturating in saline and diluted so that each cc. contained approximately

100,000 bacilli. One small loop of this suspension was streaked on each of the sixty tubes.

Weekly readings of growth were recorded over a period of four weeks. None of the tubes containing sulphocyanate showed any growth before the control tubes. Growth was visible in all at the end of one week when observed with a binocular colony microscope. It increased on all tubes until final readings were made at the end of four weeks, at which time no difference in amount or structure was noted.

Further studies were then made by removing a small amount of growth from one tube of each of the series. These were triturated in a test tube, diluted and seeded for single colony study on Steenken and Smith media (21). At the end of five weeks colony studies were made. None of these revealed other than typical and atypical Rv colonies. When these were picked out and inoculated intratesticularly into guinea pigs they produced generalized tuberculosis within sixty days.

Animal experiments: Twenty male albino guinea pigs each weighing approximately 500 gm. were selected from stock and isolated for two weeks to be certain secondary infections such as pneumonia, snuffles, otitis or streptococcic abscess were not present.

These twenty pigs were then skin tested with 5 per cent Old Tuberculin and all gave negative reactions at the end of twenty-four and forty-eight hours. They were then divided into two equal groups.

The sulphocyanate level was then determined on each group of animals. It was found impossible with the present method to determine the sulphocyanate level of each guinea pig individually because of the small amount of blood available. Therefore, 3 cc. of blood was removed from the left heart of each guinea pig and pooled to make a total of thirty cc. for the whole group of ten animals. The method used was a modification of Schreiber's for the determination of sulphocyanates in the blood. The amount present was undeterminable in both groups at the start.

All twenty animals were inoculated subcutaneously with approximately 10,000 H37 Rv organisms. Ten were fed 0.5 cc. of a 25 per cent aqueous solution of sulphocyanates or 100 mgm. daily for a period of seven months. At the end of the first ten days after infection, the animals were again bled from the left heart; at this time the sulphocyanate level of the guinea pigs that were fed sulphocyanate was 11.5 mgm. per 100 cc. of serum which was approximately the level at which humans were kept during their treatment of hypertension. At the

end of fourteen days all guinea pigs were skin tested with 5 per cent Old Tuberculin and all reacted with necrosis measuring 10 × 10 mm., showing that all were infected.

Three months after infection, a control died of generalized tuberculosis, at which time a guinea pig that was treated with sulphocyanate was killed for comparison. This same procedure was carried throughout the experiment which was terminated eight months after infection. When both series were compared, no marked difference could be noted in the degree or type of tuberculosis or organ susceptibility.

Weight charts were also made for each group of animals. Both groups gained weight at approximately the same rate for the first three and a half months and then lost until death.

SUMMARY

Potassium sulphocyanate has been administered according to Barker's method to three patients with pulmonary tuberculosis and hypertension. In one case the tuberculosis was active; in the second quiescent; and in the third apparently cured. In all a definite hypotensive effect was produced, and in none was there any deleterious effect on the tuberculosis. Cultural experiments did not show an acceleration of growth when tubercle bacilli were exposed to concentrations of sulphocyanate comparable to those used in therapy. Guinea pigs failed to show any bad effect from sulphocyanates upon a concomitant tuberculous infection.

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A COMPARISON OF DIRECT SMEAR, FLOTATION-CONCENTRATION AND CULTURE IN SPUTUM EXAMINATION[1]

C. RICHARD SMITH

The frequency with which one or another sputum test will be positive depends on the relative numbers of tubercle bacilli present in the specimens examined. Thus the superiority of concentration and cultural tests over direct smear examination will vary according to the group of patients investigated.

A fair estimation of the efficiency of the different tests is made by Willis (1): "Experience shows that, in general, concentration methods will add about 5 per cent to the number of positive cases over direct smear examination, and that culture and guinea pig inoculation will add roughly another 15 to 20 per cent."

Sweany and Stadnichenko (2) compared the results of simultaneous direct smear and sedimentation-concentration in the examination of 1,500 sputum specimens. Sixteen per cent of the positive specimens were positive by concentration and negative by smear.

In a review of the flotation test (3), we compared the results of direct smear and flotation-concentration in the simultaneous examination of 388 sputum specimens from 159 in-patients, ex-patients and applicants. The time of microscopical examination was the same for both methods. Fourteen per cent of the smear-negative specimens and nineteen per cent of the smear-negative persons were positive by flotation.

Simultaneous flotation-concentration and culture were performed on the sputum of 200 persons by Edwards, Lynn and Cutbill (4). In a group of 100 cases of tuberculosis recently negative by smear, both tests were positive in 31; culture was positive and flotation negative in 18; flotation was positive and culture negative in 6. In a group of 100 observation cases, both tests were positive in 6; culture was positive and flotation negative in 8; flotation was positive and culture negative in 3.

The present comparison was suggested by the development of a single technique for direct smear, flotation and culture. The procedure in-

[1] From the Barlow Sanatorium, Los Angeles, California.

volved combination of a good sputum solvent and an efficient differential antiseptic. A small amount of sodium hydroxide liquefies sputum quite satisfactorily for the flotation test. But, if used in a sufficiently high concentration to destroy secondary microörganisms, it is rather detrimental to the growth of tubercle bacilli. Oxalic acid, on the other hand, is a poor sputum solvent but a relatively good differential antiseptic (5). The first step, then, was to shake the total specimen vigorously with a minimum quantity of sodium hydroxide so that all sputum particles were broken up and the contained tubercle bacilli thoroughly distributed. Finally, the optimum amount of oxalic acid to be added to the portion for culture was determined by experiment.[2]

PROCEDURE

The sputum of three days is collected in an 8 oz. bottle. A "likely particle" is selected with a wide-mouth pipette and smeared on one end of a glass slide. The remaining sputum is shaken 5 minutes in a shaking machine with an equal amount of 0.5 per cent sodium hydroxide. Two cc. of this preparation is removed and mixed with an equal amount of 2.5 per cent oxalic acid in a centrifuge tube. After incubation at 37°C. for 30 minutes, the acid mixture is centrifuged and the sediment planted on two tubes of Petragnani's medium.

The sputum-sodium-hydroxide mixture remaining in the bottle is subjected to the flotation test. It is incubated at 55°C. for 30 minutes, diluted to 200 cc. and shaken 5 minutes with 1 cc. of xylol. The creamy layer that appears at the top, after standing, is skimmed off with a pipette and spotted on the other end of the glass slide, 3 to 5 layers deep.

Direct and flotation smears on the same slide are fixed, stained by heating with carbol-fuchsin, decolorized and counterstained with one per cent picric acid.

All solutions and glassware used must be sterile.

RESULTS

Simultaneous examination by direct smear, flotation and culture was made on 304 sputum specimens from 146 persons known to have, or suspected of having, pulmonary tuberculosis. Most of the persons examined had been previously negative. Ninety-four of them had under-

[2] Edwards, Lynn and Cutbill shook the sputum with an equal amount of 0.5 per cent sodium hydroxide. Five cc. of this removed for culture was treated with 4 cc. of 25 per cent sulphuric acid. Flotation was carried out on the remainder.

gone some form of collapse therapy. Ninety-five were sanatorium patients, 41 were ex-patients and 10 were applicants. There were 20 cases of arrested tuberculosis; 10 cases were apparently cured; and 14 had no clinical disease.

TABLE 1

Persons tested

	NUMBER	PER CENT OF TOTAL PERSONS	PER CENT OF POSITIVE PERSONS
Total	146	100.0	
Positive	63	43.1	100.0
Direct smear positive	18	12.3	28.5
Flotation positive	44	30.1	69.8
Culture positive	56	38.3	88.8
Flotation or culture or both positive	63	43.1	100.0
Smear negative, flotation positive	27	18.4	42.8
Smear positive, flotation negative	0		
Smear negative, culture positive	41	28.0	65.0
Smear positive, culture negative	3	2.0	4.7
Flotation negative, culture positive	18	12.3	28.5
Flotation positive, culture negative	7	4.7	11.1

TABLE 2

Specimens examined

	NUMBER	PER CENT OF TOTAL SPECIMENS	PER CENT OF POSITIVE SPECIMENS
Total	304	100.0	
Positive	96	31.9	100.0
Direct smear positive	19	6.2	19.7
Flotation positive	60	19.7	62.4
Culture positive	85	27.9	88.5
Flotation or culture or both positive	96	31.9	100.0
Smear negative, flotation positive	41	13.1	42.7
Smear positive, flotation negative	1	0.3	1.0
Smear negative, culture positive	70	23.0	72.9
Smear positive, culture negative	4	1.3	4.1
Flotation negative, culture positive	39	12.8	40.6
Flotation positive, culture negative	11	3.6	11.4

For the purposes of this comparison all direct and flotation smears showing one or more typical acid-fast bacilli after 3 minutes' examination are called positive.

DISCUSSION

The culture technique used here shows at least a theoretical advantage over the oxalic acid method of Corper and Uyei (5). In the latter procedure, the sediment obtained is so large that only a small amount of sputum may be cultured conveniently, usually about 1 cc. Obviously, tubercle bacilli may be present in only one or two small particles of a given specimen, and these may not be included in the sample selected for culture. Our technique, on the other hand, provides for distribution of tubercle bacilli throughout the specimen so that the portion removed for culture is more likely to contain some bacilli. This method was found capable of yielding growth from sputum containing as little as 10^{-9} mgm. of tubercle bacilli per cc.

It may be thought that culture is given an unfair advantage in this comparison because direct and flotation smears were examined only three minutes. When the flotation smears were examined ten minutes each, 8 additional specimens were found positive. For 5 of these specimens the culture was positive and for 3, negative.

Our results show a marked superiority for flotation and culture over direct smear examination. The superiority of culture over flotation, however, is not so marked. I believe this is an indication of the efficiency of the flotation test rather than of the deficiency of the culture method.

That culture does not always demonstrate tubercle bacilli present in the sputum is apparent. Eleven culture-negative specimens were positive by flotation and 4 by direct smear. In one instance the culture was grossly contaminated. In another the tubercle bacilli were believed to be dead. There is a possibility that acid-fast saprophytic microörganisms were mistaken for tubercle bacilli in some of the direct and concentration smears. Against this is the fact that direct and flotation tests were positive exclusively for persons with known clinical tuberculosis. Arrested and apparently cured cases, as well as those without clinical tuberculosis, were consistently negative.

But we do know that living, virulent tubercle bacilli may fail to grow on culture. The same specimen may be negative by culture and positive by guinea-pig inoculation; or it may be positive by culture and negative by inoculation. Of course, in dividing a specimen for two different tests, it is possible that all the tubercle bacilli present will be contained in one of the portions. It is more likely that the special conditions of culture are sometimes unfavorable for growth or that the microörganism concerned is refractory to the regular culture procedure.

The culture and flotation tests, then, are overlapping and supplementary. Culture is frequently positive when flotation is negative; flotation is occasionally positive when culture is negative. Taken together the two tests accounted for all the positive results obtained in this survey. Furthermore, flotation contributes the advantage of giving immediate results; culture that of being more objective and more dependable. The combination of the two methods in a single technique, with little increase in difficulty, is a definite improvement in our sputum examination program.

SUMMARY

1. A single technique is described for the simultaneous examination of sputum by direct smear, flotation-concentration and culture.

2. A comparison is made of the results of simultaneous direct smear, flotation and culture in the examination of 304 sputum specimens from 146 persons.

3. Sixty-three persons were positive: 28.5 per cent by direct smear, 69.8 per cent by flotation and 88.8 per cent by culture.

4. Ninety-six specimens were positive: 19.7 per cent by direct smear, 62.4 per cent by flotation and 88.5 per cent by culture.

5. Culture and flotation are overlapping and supplementary. Each test is capable of demonstrating tubercle bacilli not detectable by the other. The routine performance of the two tests by a single technique is worth while.

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PLOMBAGE IN PULMONARY TUBERCULOSIS[1]

A Progress Report Based on Animal and Clinical Experiments with an Agar-Agar Compound

J. W. CUTLER

Plombage might be a procedure of wide usefulness in the surgical treatment of pulmonary tuberculosis but to date has been employed in a limited number of cases only, and with indifferent results, largely because of the lack of a suitable compound that can fulfill the mechanical requirements of the operation.

These requirements and the reasons for them can be briefly stated as follows:

1: The compound must be nontoxic. Obviously it must not produce constitutional symptoms.
2: It must be almost nonirritating. Although a slight degree of local irritation is desirable to encapsulate the compound and anchor it to the surrounding structures, the irritating factor must be mild and not interfere with primary healing of the wound, nor be a source of future concern.
3: It must be stable. Since the compound must remain in the body indefinitely or until such time as the diseased area in the lung has healed, it must not be absorbed or undergo deterioration or chemical change.
4: It must be incapable of supporting animal or vegetable life. Its chemical composition should be such as not to serve as a source of energy for bacteria or other microörganisms.
5: It must be sterilizable. It should be possible to autoclave the compound or otherwise render it sterile without changing its composition.
6: It must be of low specific gravity. The compound should be sufficiently light in weight so that it will not gravitate or give the patient a sense of heaviness or discomfort.
7: It should be radiopaque. It should be easy to visualize and differentiate the compound from all surrounding structures by means of the X-ray. This makes possible an accurate check on the efficiency of the operation, and should help in the development of good operative technique.
8: It should be plastic, preferably semiliquid, when first introduced into the

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body. The compound should act in a passive manner when splinting the lung and fill the extrapleural space which has been created for it after the lung has been collapsed by the proper surgical technique in the same manner as concrete fills a form. This feature is essential to the safety of the operation.
9: It should solidify at slightly above body temperature within a reasonable time so as not to delay the progress of the operation on the one hand nor hurry the operator on the other.
10: Once solidified, it should remain solid in the body under all conditions. A solid compound is a much more efficient splint than semisolids or liquids. A certain amount of elasticity is, however, desirable.
11: It should not encourage the invasion of fibroblastic tissue.

It becomes apparent that the ideal compound for plombage must have many qualifications and it is for this reason that one substance after another has been tried and found wanting. Fat (Tuffier), muscle (Archibald), paraffin (Baer), gauze (Graham, Lange), and liquid petrolatum are only a few of the many substances that have been used. Paraffin has met with most favor, but it is far from the ideal.

Composition of Agar-Agar Compound

During the summer of 1933 I discussed the problem with the chemical research staff of the S. S. White Manufacturing Company. They showed me "elastic compound," a commercial product which they had developed for making dental impressions. When I observed the working properties of this compound, my interest in its possibilities for plombage was aroused. The composition of elastic compound as given by the manufacturer is approximately as follows:

	per cent
Agar-agar	13
Waxes and vegetable oils	6
Vegetable fibres	0.1
Pigment	5
Flavoring substance	0.3
Antiseptic	0.01
Water to make	100

This compound obviously could not be used for plombage. I was informed, however, that it could be prepared in a highly purified form, and requested that samples be furnished me for experimental purposes. All the material used in this work was prepared in the research department of the S. S. White Dental Manufacturing Company under the direction of Mr. W. S. Crowell, supervising chemical engineer, who kept

in close contact with the clinical aspects of the work. The present composition of the plombage compound is as follows:

	per cent
Agar-agar	13
Paraffin, sufficient to lubricate the mass	6
Barium sulphate	5
Phenyl mercuric nitrate	0.000,1
Salt	0.5
Water to make	100

This agar-agar compound is a reversible hydrocolloid. A hydrocolloid is a substance dispersed in water in the colloidal state, intermediate in character between suspension and true solution. Glue is a familiar example of a substance in a hydrocolloidal state. A reversible hydrocolloid is one which can be caused to liquefy and to set or solidify by the alternate application of heat and cold, at the will of the experimenter.

At ordinary temperatures this compound is firm and elastic. When heated to about 212°F. it becomes a thick liquid. When cooled, it does not set or gelatinize at once, particularly if worked while cooling. The time of gelation depends upon the temperature. At 120°F. it will remain liquid for 45 minutes, at 100°F. for 10 minutes, but when the temperature is reduced to 60°F. it solidifies in half a minute. This makes it possible, after liquefying the compound by autoclaving, to reduce it to body temperature or slightly above, and fill the extrapleural space with approximately ten minutes working time available, before solidification.

The barium sulphate makes it radiopaque and gives the compound a certain degree of body. The small quantity of paraffin lubricates the mass and prevents it from adhering to the surrounding structures. The phenyl mercuric nitrate acts as a powerful, nonvolatile antiseptic preventing the growth of bacteria and molds. The salt solution gives it the necessary osmotic properties.

At body temperature this compound is a stable, nontoxic, slightly irritating substance. It is not absorbed, and in time becomes encapsulated by fibrous tissue in the same manner as any foreign body. It can be removed at the will of the operator.

Results with Agar-Agar Compound A

In the first experimental formula (compound A), there was no sodium chloride. Metaphen was used as the antiseptic instead of phenyl mer-

curic nitrate. The agar-agar, however, was extremely pure with even less impurity than that required by the U. S. P. The formula of compound A was as follows:

	per cent
Agar-agar	15
Paraffin	4
Beeswax	2
Barium sulphate	5
Metaphen	0.2
Water to make	100

This compound had the necessary mechanical qualifications essential for plombage and was radiopaque. It would not support bacterial growth or molds and could be autoclaved.

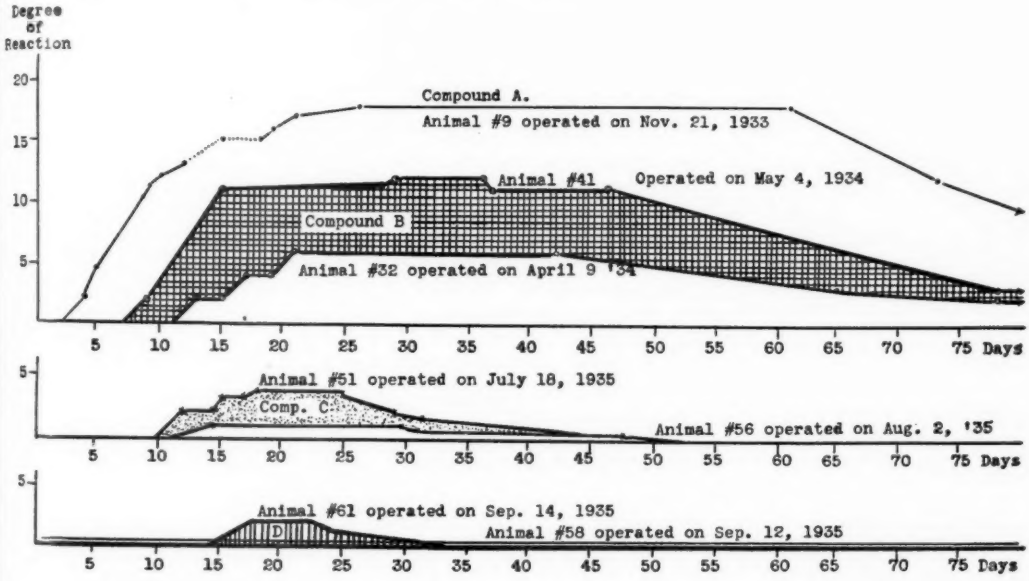

Degree of Reaction
20
15
10
5
Compound A.
Animal #9 operated on Nov. 21, 1933
Animal #41 Operated on May 4, 1934
Compound B
Animal #32 operated on April 9 '34
5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 Days
Animal #51 operated on July 18, 1935
Comp. C
Animal #56 operated on Aug. 2, '35
Animal #61 operated on Sep. 14, 1935
D
Animal #58 operated on Sep. 12, 1935

FIG. 1. Reaction in rabbit to implantation of agar-agar compound, next to parietal pleura, expressed in arbitrary units of degree of gross swelling at site of implantation.

When it was introduced into the rabbit, however, it was extremely irritating (figure 1, compound A, animal 9). With few exceptions, the wound would become angry, discharge profusely, and the compound would in time slough out. There were no constitutional signs of toxaemia.

Results with Undialyzed Agar Compound (Compound B)

The problem, therefore, was to eliminate or materially reduce the irritating properties of this compound. A series of experiments in

salt concentration were undertaken to bring the osmotic pressure of the compound into harmony with that of the body, and finally the necessary concentration of sodium chloride in the compound was determined. This materially reduced the local irritation in the experimental animal, but did not eliminate it. The wound, however, healed and a strong, thick, fibrous capsule would in time surround the compound. Between the compound and the capsule there was always considerable sterile pus, consisting chiefly of broken down polymorphonuclear cells, the result of foreign-body reaction. Phenyl mercuric nitrate was sub-

FIG. 2. Agar-agar compound implanted in rabbit, next to parietal pleura and covered by muscular layers. Note the tumor-like swelling along the anterolateral chest-wall.

stituted for metaphen, because of its greater stability during the processing of the compound.

This modified compound was placed next to the parietal pleura, in the intercostal spaces and covered by layers of muscle (figure 2). The parietal pleura was not stripped away from the ribs, as spontaneous pneumothorax with death of the animal was a frequent complication. As the purpose of the experiment was to determine tissue tolerance and particularly that of the pleura to the compound, there was no objection to this technique. The animal, therefore, had a swelling on the side

of the chest operated upon, which conformed to the size of the compound and the associated foreign-body reaction.

Although the wounds healed in all the animals operated upon, the amount of reaction varied in the different animals. In general there were two extremes. In one group the reaction was severe, becoming conspicuous on the seventh day and increasing rapidly day after day with loss of outline of the compound within the swelling until the reaction reached its peak about the fourteenth day. In a few instances the wound would break down and continue to discharge sterile pus for about two weeks and then close. Sometimes the wound would reopen again, but in time it would close and remain so. The swelling, after the height of the reaction, would no longer increase but would continue the same in size until about the forty-sixth day after operation, when it would gradually decrease. The outline of the compound would again become distinct and the latter could be felt as a firm mass surrounded by a thick, fibrous capsule anchoring it securely to the chest-wall. It could not be displaced, even by strong effort. This state of affairs was usually reached by the seventieth day (figure 1, compound B, animal 41). The animals would thrive during the entire experimental period, and lived on indefinitely until sacrificed or until they died of some intercurrent disease.

In the other groups, the swelling would not become noticeable until about the eleventh or twelfth day and would then increase gradually, until about the third week, to about half the size of the swelling in the first group, and then remain stationary until about the forty-second day, after which it would gradually reduce in size until the compound was again distinctly palpable. The entire cycle was less intense and of shorter duration. The wound would never break down and discharge. It was from every standpoint a satisfactory result (figure 1, compound B, animal 32).

In other animals the results varied between these two extremes. There was no explanation at the time for the difference except individual variation in the animals in foreign-body response.

Another series of animal experiments was undertaken to ascertain which of the component parts of the compound was responsible for the swelling, and the conclusion was reached that it was the agar-agar itself. However, since in all animals the reaction set up by the compound eventually subsided, leaving an effectively anchored compound, a cautious trial in tuberculous patients seemed justified. It was felt that

even should a discharging wound develop, it would close as it did in the experimental animal and nothing serious would happen. Furthermore, the compound could be removed.

Ten patients were subjected to operation in the summer of 1934, between June 6 and August 31. No more than 200 cc. of compound, approximately equivalent to 200 gm., was used in any one case, and in some instances the amount was as little as 100 gm. There was no attempt to select the ideal patient for plombage. With two exceptions, all had active, far advanced bilateral tuberculosis. In one the disease was acute and spreading rapidly. In three the disease was so extensive and so widespread that cure was out of the question. Artificial pneumothorax had been tried in all patients, but could not be established because of extensive adhesions. Thoracoplasty could be considered seriously in only two patients and these refused the operation. Although it was hoped to close the cavities and ultimately control the disease with the aid of plombage and such supplementary collapse measures as could be applied, control of the disease and negative sputum were not considered at the time as likely to be quickly attainable, or essential objects of the study. The immediate problem was to ascertain if the compound could be tolerated by the average patient who potentially could be helped by plombage.

The results, therefore, in these ten patients must be judged solely by the patient's toleration of the agar compound and the expectation of healed wounds, without serious foreign-body reaction, in a sufficiently large number of patients to warrant further use of the operation.

The wound results varied widely. In only one case was there a healed wound with no subsequent foreign-body reaction. This case will be described in greater detail later on. It is in order to point out, however, at this time that this patient was observed for a period of 34 months and during this time there was no clinical or X-ray evidence of foreign-body reaction. The patient had no sensation of weight or dyspnoea. This was the only case in this series of ten in which the result was entirely satisfactory. In two patients the foreign-body reaction was of moderate degree and did not become noticeable clinically until about the third week, when the incision began to swell and finally broke down, leaving the patient with a small discharging sinus. In one of these patients the fistula ultimately closed six months after operation. Both patients seemed to be definitely benefited by the plombage, and there was no reason to believe that the small sinus left was seriously detrimental.

In three patients the wound discharge was considerable and made its appearance within the first week or ten days. Small pieces of compound could be detected in the discharge. In one patient considerable compound sloughed out within the first two weeks and the wound healed promptly. Some of the compound, however, is still present in the body at the time of writing (January, 1938), forty months after operation, and is giving the patient no trouble whatsoever. In the other two patients the fistula refused to heal and there was a persistent moderate discharge which required change of dressings about once a day. The collapse obtained by the plombage, however, was of sufficient benefit to the patient to warrant leaving the compound in. Both of these patients have since died because of their advanced tuberculosis.

In four patients the foreign-body reaction became definite on the third or fourth day. The wound appeared swollen and red and discharged profusely as soon as opened. Pieces of compound could be detected in the discharge. No microörganisms were found either by culture or smear in pus obtained aseptically. The acute phase subsided within a week and the patients were left with a badly discharging fistula which refused to heal even though the compound was removed. Three of these patients are dead, 3, 5 and 15 months respectively after operation, their death probably hastened by the discharging wound, which became secondarily infected. The other patient left my observation eleven months after operation, at which time the wound was draining worse than ever in spite of removal of the compound. In all probability he is dead. It may be of interest to note that he was a confirmed alcoholic.

To summarize the condition of the wounds, there was one excellent result, two good results, three fair results and four poor results. In the latter the discharging wound was such an obviously serious objection that further work in man was discontinued.

All the phenomena except one observed in the experimental animal could be duplicated in the human patient. In the rabbit all wounds healed, including those with temporary fistula. In the human, however, once a fistula developed, it almost invariably refused to heal. It was apparent that the human tuberculous patient was more sensitive to the agar compound than the experimental animal and that more work was necessary in order to modify the irritating properties of the compound. The single excellent result and the two good results were encouraging and seemed to indicate that the effort was worth while.

Results with Dialyzed Agar Compound (Compound D)

In the spring of 1935, a new series of animal experiments was undertaken to test the irritating properties of agar-agar compound that had been purified by protracted dialysis. Since the irritating property of the compound appeared to be due to the agar it was thought that the maximum attainable purification of the agar was indicated. When dialyzed agar-agar was used and no other change made, there was a distinct decrease in foreign-body reaction in the animal. There were still variations, but results were distinctly better than the best results with undialyzed agar-agar. The compound could always be palpated in the animal through the surrounding reaction and the swelling would decrease by the end of the third week, with no sign of reaction whatever after the forty-seventh day.

The entire cycle of foreign-body reaction was considerably reduced in severity and duration. In some animals the result almost approached the ideal in that there was little noticeable foreign-body reaction. The range between extremely good and extremely bad result was materially narrowed (figure 1, compound C, animals 51 and 56). By following the same lead and dialyzing the agar-agar a little longer (three weeks), a compound was obtained which produced no palpable foreign-body reaction (figure 1, compound D, animals 58 and 61).

It was therefore decided to employ the compound again in human patients. The first patient in the new series was operated upon on November 15, 1935, and the result was encouraging. The wound healed promptly by first intention and has remained healed to this day with no clinical or X-ray evidence of foreign-body reaction (December, 1937, 25 months after operation). Although the cavity is still open and the sputum positive, the cavity is reduced in size and the patient improved clinically. In all, nine patients have been operated on in the second series between November, 1935, and January, 1936, with the following wound results:

(*1*) One patient, referred to above, had a healed wound with no clinical or X-ray evidence of early or late foreign-body reaction.

(*2*) In three patients there was delayed healing of the wound with a minor fistula for 5, 6 and 8 months respectively, requiring change of small dressings about once in 24 hours. All wounds ultimately healed. Two of these are definitely improved to this day (January, 1938). The other patient died of cardiorenal disease and lead poisoning 11 months after operation and 6 months

after the wound had completely healed. As far as the tuberculosis was concerned he was definitely benefited by the operation.

(*3*) One patient has a small fistula with little discharge from the wound, requiring change of dressing about once a week. The sinus has persisted now for 18 months, but seems of little clinical significance, although culture of the discharge on June 16, 1936, was positive for tubercle bacilli. No other micro-organisms were found.

(*4*) Two patients had moderately discharging sinuses requiring frequent change of dressings. Although both patients are dead, their death was due to the far advanced character of the tuberculosis. The discharging sinus could be counted as little of a contributing factor. One of these patients had advanced intestinal tuberculosis at the time of the operation.

(*5*) Two patients had profusely discharging sinuses which became secondarily infected. One of these cases was complicated by a haematoma. In this case the wound healed promptly after operation and the result seemed ideal. On the tenth day there was considerable bulging at the upper end of the wound and upon opening it 200 cc. of dark brown fluid was removed. There was no evidence of foreign-body reaction. A few days later, however, there was yellowish discharge with expulsion of several small pieces of compound. The discharge became gradually worse in spite of irrigations and removal of the compound. The patient died of toxaemia from secondary infection of the wound, June 5, 1936, seven months after operation. What the result would have been without the complicating haematoma is difficult to say. The other patient also died of toxaemia resulting from secondary infection of the badly discharging wound.

It will be noted that healed wounds were obtained in four patients of the new series of nine, or in 45 per cent, and that in another patient the wound, while not ideal, is certainly satisfactory. This is in contrast to two healed wounds, or 20 per cent, and the one wound with a minor fistula (satisfactory result) in the first series of ten patients. Because of the poor results obtained in the patients with badly discharging sinuses further work on the human has been discontinued until more progress can be made in modifying the irritating qualities of the compound.

Continued efforts along this line have not been fruitful although work is still in progress. It is possible that if this operation were restricted to earlier cases better results could be obtained, as unquestionably the condition of the pleura must play an important rôle in the formation of the wound fistula. In some cases (advanced tuberculosis) the overlying pleura is studded with tubercles and will not tolerate any foreign body.

THE CLINICAL VALUE OF PLOMBAGE

It was not the intention of this report to dwell on the effect of the operation on the tuberculosis, as the disease in the patients selected was entirely too far advanced to hope for cure. The problem was to study the reaction of the human being to the implantation of the agar-agar compound, and give the patient as much benefit as might be obtained by collapse of cavities otherwise noncollapsible. It was obvious that should the compound be well tolerated, good results must follow in the same manner that good results follow other forms of successful collapse therapy such as pneumothorax, oleothorax or thoracoplasty. On the other hand it seems warranted to place on record the general impression of the operation based on the nineteen operations performed to date. It is an operation well tolerated by the so called poor surgical risk, and can be carried out under local anaesthesia. There was not a single death in the entire series of the nineteen advanced cases which could be attributed to the operation itself, and with good technique one should be able to close fairly large cavities, by stage procedures if necessary. There is no mutilation of the chest-wall. It seems the ideal operation for that large group of patients in whom pneumothorax cannot be established because of extensive adhesions, in whom phrenic nerve operation has failed or is a useless undertaking, and who refuse thoracoplasty, or in whom it is distinctly contraindicated because of age, character of the lesion, or condition of the contralateral lung. It is estimated that this group approximates 25 per cent of the present tuberculous population. It should be emphasized that plombage is not to be expected to cure all of these or that it will be sufficient in itself, but in combination with other collapse therapy procedures it should materially improve the prognosis of this group. Of the nineteen advanced cases in this report, nine, or 47 per cent, appeared to be distinctly benefited by plombage.

FIG. 3. Case *A. C.* Condition of lungs before plombage. Note large cavity in left upper with consolidation in left lower lobe.

FIG. 4. Case *A. C.* Shortly after plombage operation on left; 200 gm. of agar-agar compound was introduced extrapleurally, and the cavity partly closed.

FIG. 5. Case *A. C.* Five months after plombage operation. Apical cavity partly closed. Appearance of new cavity in area of consolidation in left lower lung field.

FIG. 6. Case *A. C.* Nine months after plombage and four months following left phrenic evulsion. The lower lobe cavity is closed and the patient improved clinically. Note beginning descent of the agar compound.

FIG. 3

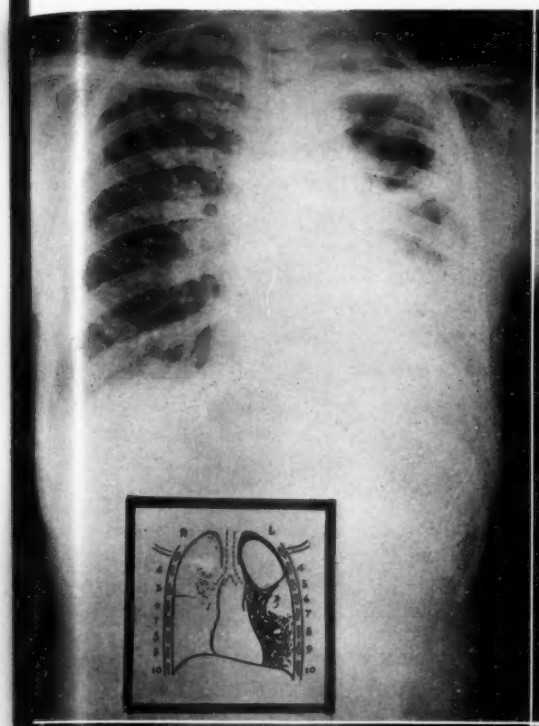


FIG. 4

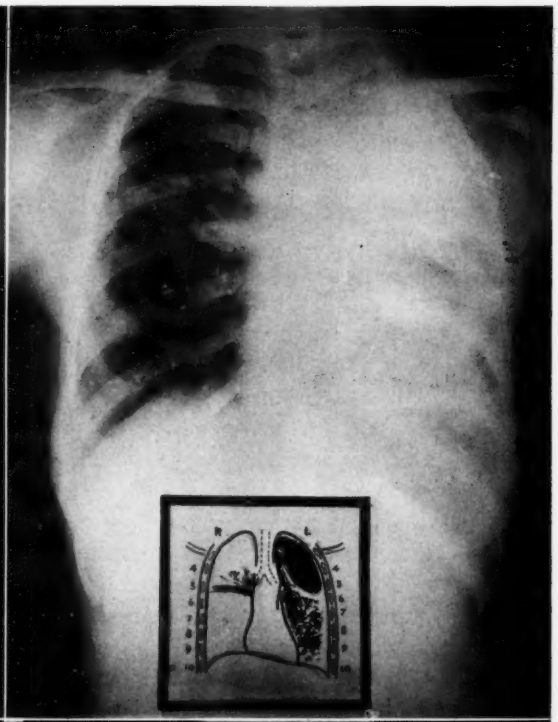


FIG. 5

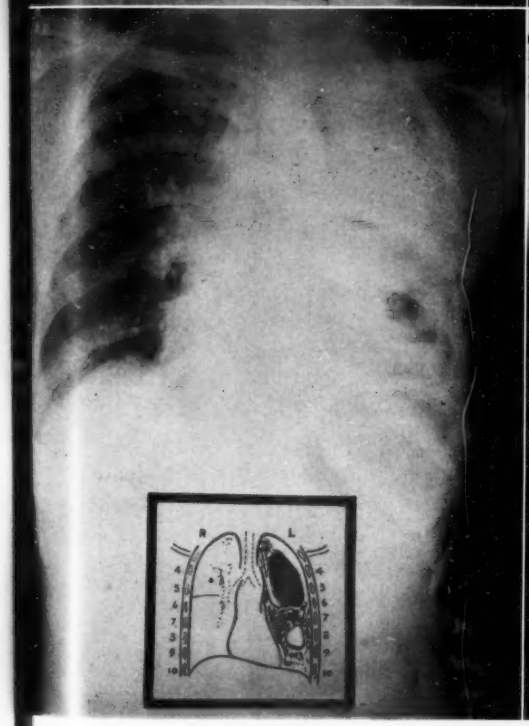
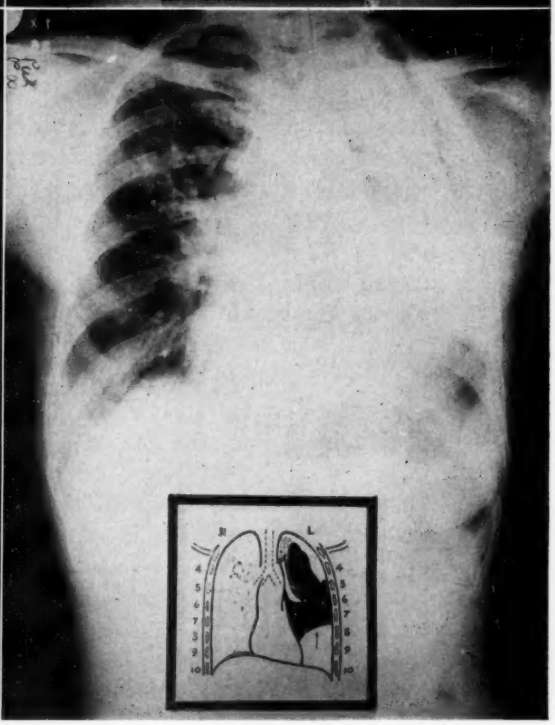


FIG. 6



FIGS. 3–6

Although the results here recorded are presented simply to indicate progress in the development of a nonirritating compound suitable for plombage, two case reports are presented to illustrate the possibilities in this form of therapy.

A. C., a colored female, 46 years of age, first came under observation at the Henry Phipps Institute in November, 1935. In the X-ray film there were unequal demarcated medium-size spots in the upper two-thirds of the right lung, densest mesially, and unequal consolidation throughout the left lung, with a large cavity, 9 x 4.8 cm., in the left upper and scattered small cavities below (figure 3). Her weight was 80 per cent of normal. Blood sedimentation was rapid. The sputum was positive for tubercle bacilli. Pneumothorax on the left could not be established because of adhesions. By December 3, 1935, the patient had lost four pounds in weight and the cavity at the left apex was considerably increased in size. She was not suitable for thoracoplasty and plombage of the left apex was performed on December 18, 1935. Approximately 200 gm. of agar compound was introduced through a posterior incision (figure 4). The cavity was considerably reduced in size, but not closed. There was a small draining fistula following operation which required infrequent change of dressings and which persisted seven months, but finally closed and has remained closed to this day (August, 1937). Within the five months following operation, a large cavity developed in the left lower lung field where previously there had been several small cavities and considerable consolidation (figure 5). The entire lung area was breaking down; yet the patient appeared clinically in fairly good condition. A left phrenic evulsion was performed on June 2, 1936, and a good rise of the diaphragm obtained (figure 6). The result that followed the phrenic operation has been interesting and has been observed in other patients in this series. It seems that release of the diaphragmatic pull associated with release of the apex following the plombage resulted in increasing atelectasis, and the left lung was shrunken to a small mass occupying about one-fourth of its original size. The descent of the apex was followed by simultaneous descent of the agar compound, which finally took a position in front or behind the lung and could just barely be distinguished from the lung itself (figure 7). In the meantime the patient improved clinically. Her cough and expectoration have greatly diminished. Her weight increased from 102 pounds to 108 pounds (79 per cent of normal). Sputum for examination is at present (October, 1937) obtained with difficulty and is either Gaffky one or negative. The right lung has also materially improved. As stated, the wound has been healed since July, 1936.

Comment: The result obtained in this patient, observed now for a period of 22 months, has been gratifying and has fulfilled all reasonable

expectation. The patient before operation had active, destructive tuberculosis involving both lungs. She was 46 years old and not a suitable subject for a major thoracoplasty. Pneumothorax could not be established and the prognosis was extremely bad. As matters now stand, plombage reënforced by a phrenic evulsion has given her relief of symp-

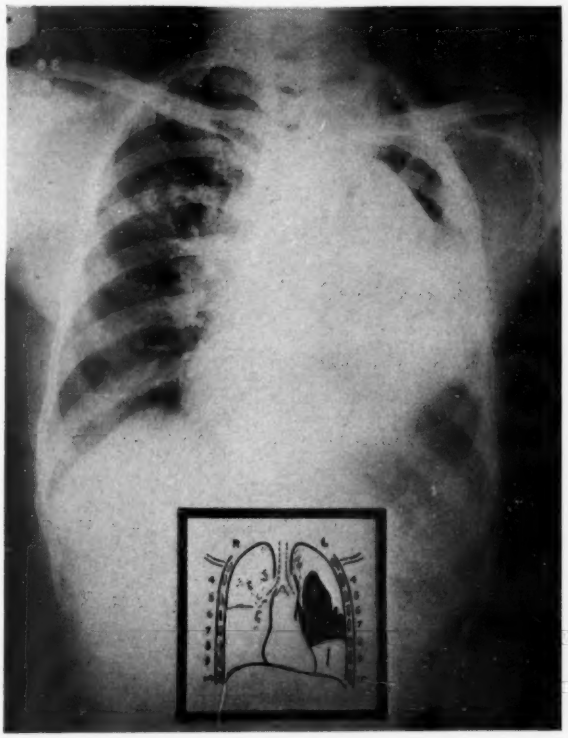
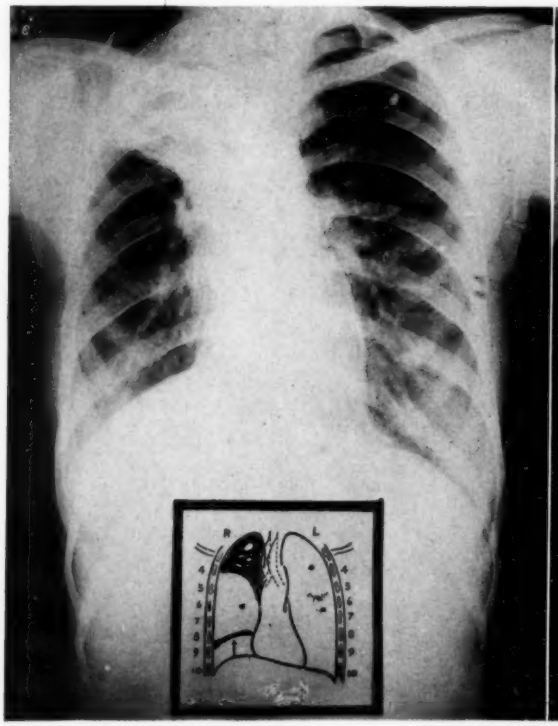


FIG. 7. Case *A. C.* One month later. There has been a marked descent of the plombage compound, probably due to a shrinkage of the left lung resulting from the general relaxation of the lung following apicolysis and phrenic evulsion. Whatever the true interpretation, the X-ray appearance was accompanied with clinical improvement which has persisted to the present (August, 1937). X-ray examination June 29, 1937, 8 months after the above film, is practically identical.

toms, and apparently prolonged her life, and gives promise of permanently arresting her tuberculosis.

C. D., a white female, 23 years of age, had had chronic tuberculosis of the right upper lobe for 41 months at the time plombage was considered in July, 1934. The disease consisted of dense infiltration in this lobe and strands

with multiple cavities, the largest 2.5 cm. in diameter. There were also a few insignificant spots in the upper third of the left lung (figure 8). Her sputum was positive for tubercle bacilli. The patient's weight was 81 per cent of normal. Blood sedimentation was only moderately rapid, with an index of 15 mm. Pneumothorax had been attempted but could not be estab-



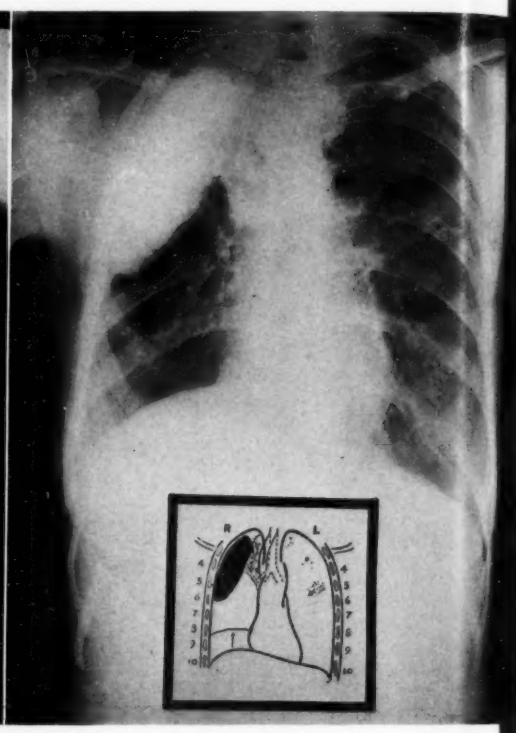


FIG. 8 FIG. 9

FIG. 8. Case *C. D.* Condition of lungs before plombage. There is chronic disease with cavity formation, involving the right upper lobe. A few spots are also present in the middle lung field on the left.

FIG. 9. Case *C. D.* Twenty-seven months after plombage operation in July, 1934, and shortly before the appearance of widespread disease in the left lung. The sputum has been negative since operation and frequent X-ray examination indicated a well collapsed right upper lobe.

lished. A phrenic evulsion was done eight months previously and, although a good rise of the diaphragm was obtained, it did not influence the disease. The sputum continued to be positive for tubercle bacilli.

Thoracoplasty was suggested, but the patient refused. Plombage on the right side was performed on August 11, 1934, and an excellent result obtained.

The wound healed by first intention. There was no clinical or X-ray evidence of foreign-body reaction, no fistula, no dyspnoea or sensation of weight. The sputum became negative immediately following the operation, and she was discharged from the hospital on the eighth day. Her strength was good and she shortly returned to work in a cigar factory. Her health continued excellent and clinically her tuberculosis was definitely under control. Figure 8 illustrates the lesions in the right upper lobe before operation, and figure 9, 27 months after operation.

In the film of November 3, 1936 (figure 9), for the first time new disease was noted in the left lung, consisting of soft spots chiefly in the inner half of the middle third. Her weight at that time was 86 per cent of normal. The sedimentation rate was 13. There was no cough or expectoration. The patient was advised of this new disease and pneumothorax was considered but postponed. She was asked to report for observation at frequent intervals, but unfortunately failed to keep her appointments because she felt too well. Within three months, however, she was much worse and was admitted to the Jefferson Hospital because of severe haemoptysis. X-ray examination of her chest on March 29, 1937 at the hospital revealed widespread disease throughout both lungs with scattered recent cavities in the left lung. The patient died on May 3, 1937. Through the courtesy of the pathologic staff of the Jefferson Hospital, the lungs were referred to Dr. Esmond R. Long of the Henry Phipps Institute for examination. His report is here given in brief:

The left lung is larger than the right. The right upper and middle lobes are almost completely collapsed, and the lower lobe is collapsed to a considerable extent.

Anatomical diagnosis: Chronic bilateral, ulcerative and fibroplastic tuberculosis of the lungs. Marked collapse of the upper and middle lobes of the right lung with partial closure of several cavities and extensive fibrosis of the upper lobe. Encapsulated plombage compound lateral, extrapleurally, to upper third of right lung. Caseopneumonic and scattered bronchogenic tuberculous infiltration of the left upper lobe, and to a lesser extent of the left lower and right middle and lower lobes. Calcified tuberculous primary complex in the lower lobe of the right lung and the right hilar lymph nodes.

Histology: Sections from the lung tissue (right apex) below the plombage compound show extensive atelectasis and widespread linear scars parallel with the plane of atelectasis. Occasionally there is lymphocytic infiltration around the scars, but for the most part the latter consist of old collagenous connective tissue adjoining collapsed lung, with no signs of accompanying inflammation. Very rarely a contracted densely staining giant cell and small collection of epithelioid cells are found in the scarred regions. Comment: Extensive healing of a previously widespread tuberculous lesion. The plombage compound is homogeneous and shows no change. Left lung—upper lobe: Ex-

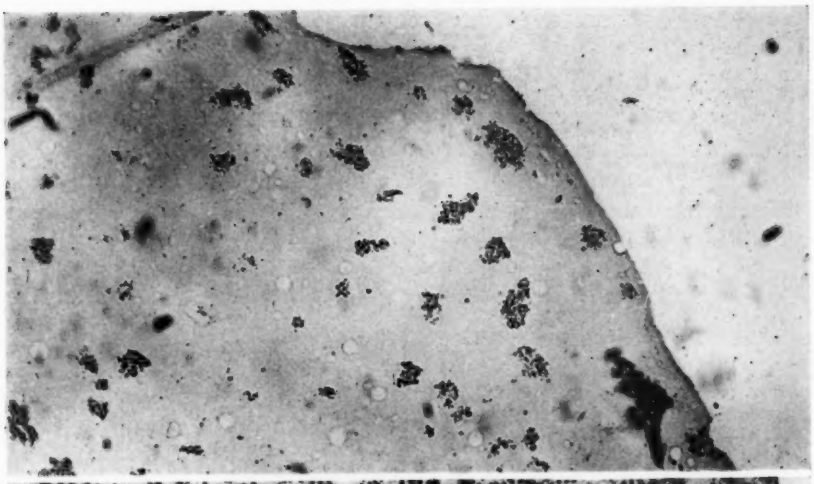


FIG. 10

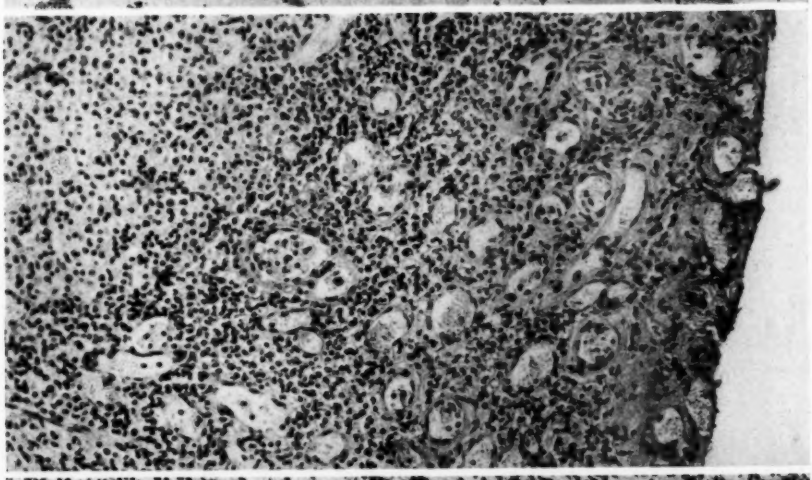


FIG. 11

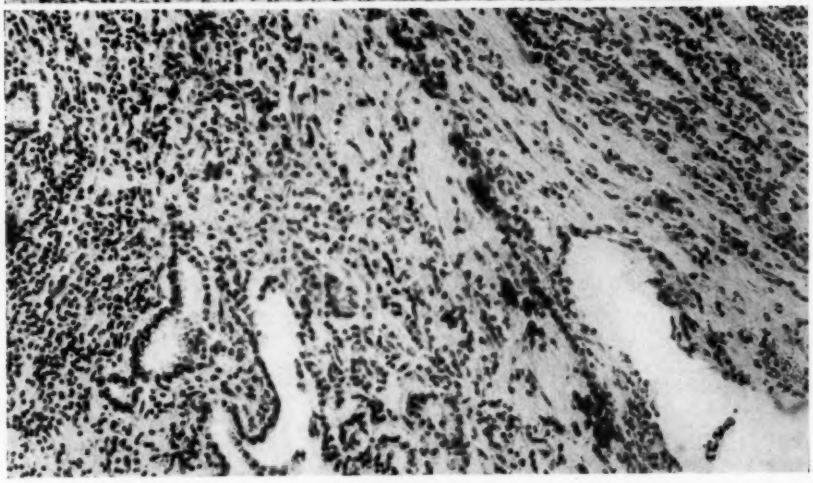


FIG. 12

FIGS. 10–12

tensive ulcerative tuberculosis. The cavities are lined by a thick suppurating layer containing many tubercle bacilli. The granulation tissue around the cavities is extensive. Elsewhere there is emphysema.

It is apparent that in this case the plombage was a successful procedure in bringing the disease in the right upper lobe under control. This was accomplished without mutilation of the chest-wall, shock or operative risk. It was therefore superior to a thoracoplasty, which in this case, in contrast to the first case, could have been carried out.

In spite of the obvious advantages that may be derived from plombage, unless a compound can be developed of such mild local irritating properties that it will not interfere with wound healing, nor cause late sequelae resulting from foreign-body reaction, the operation can have only limited application. Thoracoplasty in its present stage of evolution offers many patients an excellent chance for recovery with a low mortality rate. If, however, thoracoplasty is definitely contraindicated, and other collapse procedures cannot be applied or have failed, plombage does offer the patient some chance, and is worth considering.

SUMMARY

Since the summer of 1933 experiments have been made with an agar-agar compound apparently answering many of the requirements for successful plombage better than other substances used heretofore. The compound, composed of agar-agar, paraffin, barium sulphate, salt solution and an antiseptic (phenyl mercuric nitrate), is nontoxic, radiopaque, sterilizable and has practically all the essential mechanical qualifications. It has, however, one apparent drawback. Although in the experimental animal (rabbit) this compound is well tolerated and no troublesome foreign-body reaction results, in man it may set up too strong a local foreign-body reaction resulting in minor fistulas or even profusely discharging sinuses.

FIG. 10. Compound removed at necropsy from patient with small draining sinus 19 months after plombage. The small collections of dots scattered throughout the section represent the barium sulphate incorporated in the compound. The dark mass in the lower right corner is a colony of bacteria. There is no leucocytic or fibroblastic invasion of the compound.

FIG. 11. Granulation tissue around compound from same patient. The tissue is highly vascular and in no places is there frank suppuration. Most of the cells are lymphocytes. Tubercle bacilli were not found in the granulation tissue in this case.

FIG. 12. Atelectatic lung tissue below compound in same patient. The band of scar tissue represents a region of old tuberculous infiltration.

After extensive trial in the experimental animal, agar compound was employed cautiously, extrapleurally, to close cavities and control tuberculous disease in nineteen patients with far advanced, active tuberculosis, in whom other measures had failed or could not be instituted. Ten of these patients were subjected to the operation in the summer of 1934 with undialyzed agar compound (compound B), and nine in the fall of 1935 with dialyzed agar compound (compound D). Nine of these patients, or 47 per cent, appeared to be distinctly benefited by the procedure.

In the first series of ten patients (plombage with compound B) the condition of the plombage wounds was as follows: healed wounds, 2 (20 per cent); minor fistula, requiring infrequent change of dressing, and clinically of little significance, 1 (10 per cent); moderately discharging sinuses, clinically undesirable, 3 (30 per cent); profusely discharging sinuses, clinically unsatisfactory, 4 (40 per cent).

In the second series of patients (plombage with compound D) the wound results were strikingly superior, with twice as many good results. The condition of the nine plombage wounds were as follows: healed wound, 4 (45 per cent); minor fistula, 1 (11 per cent); moderately discharging sinuses, 2 (22 per cent); profusely discharging sinuses, 2 (22 per cent).

Because of the poor results obtained in patients with badly discharging sinuses, further clinical application has been discontinued until more progress can be recorded in modifying the local irritating properties of the agar compound. Continued efforts along these lines have not been fruitful, but work is still in progress. It is possible that, if the use of the agar-agar compound were restricted to earlier cases, better results could be obtained.

Acknowledgment is made to the S. S. White Dental Manufacturing Company for supplying the samples of purified agar compound used in this work and for allowing the publication of data on them.

Acknowledgment is also made to Alfred Kisseleff, V.M.D., for his valuable assistance with the animal studies.

INTRACUTANEOUS TUBERCULIN TEST[1]

A Clinical Investigation of Some Factors Involved

M. PARETZKY

The importance of the correct evaluation of the influence of various factors on the outcome of the intracutaneous tuberculin (Mantoux) test is obvious to every worker applying this test. He is frequently confronted with the question whether the reading of the test is distorted to a degree of unreliability by these factors. Many workers have presented their observations on the influence of some factors, as light, heat, seasonal variations of the climate, certain drugs, different brands of tuberculin, etc. The present report is limited to an investigation of (*1*) the variation in the regional skin hypersensitiveness, (*2*) deterioration of tuberculin, (*3*) "tenacity" of tuberculin, (*4*) the size of the wheal, and (*5*) the application of alcohol.

THE VARIATION OF THE REGIONAL SKIN HYPERSENSITIVENESS

Originally it was not planned to include the investigation of this factor in the present report. But, as the work on other factors progressed, it became more and more evident that the correct evaluation of the significance of the variation of the regional skin hypersensitiveness is of prime importance as a "control" in the proper interpretation of the influence of the other factors. Finally it became clear that taken *per se*, even without any relation to other factors, the variation of the regional skin hypersensitiveness is a factor of independent and great importance to the extent of justifying its being investigated as fully as possible.

Three solutions of Old Tuberculin manufactured by Cutter were used in these series: 1:1,000, 1:100,000 and 1:10,000,000. The first two solutions were used as delivered by the manufacturer. The last was prepared by us by diluting the 1:100,000 solution one hundred times; as a diluent we used Baxter's distilled sterile water, fractionated and protein-free, to which a sufficient amount of phenol was added to make up a 0.5 per cent solution. Separate new tuberculin syringes were used for each

[1] From the Tuberculosis Division of the Los Angeles County Health Department, Los Angeles, California.

of the three solutions. An equal dose of 0.1 cc. of the reagent, taken with the same special syringe from the same vial, was applied to the symmetrical regions of the anterior surfaces of both forearms. One hundred persons were tested in the described manner with each solution, or a total of three hundred "double" tests were made in this series. The readings in this and all following series reported in this paper were made by the nurses of the Los Angeles County Health Department, who were instructed to designate the degrees of the reactions in accordance with the standards suggested by the National Tuberculosis Association.

As it can be seen from table 1 most of the reactions were equal on both forearms. The percentage of equal reactions was 71.6 per

TABLE 1

A study of the variation of skin hypersensitiveness to tuberculin on both forearms

DILUTION	EQUAL REACTIONS ON BOTH FOREARMS		THE RIGHT FOREARM REACTED STRONGER						THE LEFT FOREARM REACTED STRONGER						TOTAL OF ALL TESTS IN THE SERIES	
			Total of tests in which both forearms reacted		Right forearm reacted, left did not		Total of all tests		Total of tests in which both forearms reacted		Left forearm reacted, right did not		Total of all tests			
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
1:10,000,000	77	77	7	7	5	5	12	12	5	5	6	6	11	11	100	100
1:100,000	70	70	6	6	5	5	11	11	7	7	12	12	19	19	100	100
1:1,000	68	68	21	21	2	2	23	23	7	7	2	2	9	9	100	100
Total.....	215	71.6	34	11.3	12	4	46	15.3	19	6.3	20	6.6	39	13	300	100

cent for the entire series. A large proportion of the tests, 28.3 per cent of the total, has resulted in decidedly unequal reactions on both forearms. Comparing the figures for the unequal reactions we can see that the right forearm has on the whole reacted somewhat more strongly than the left, yeilding for the whole series a total of 15.3 per cent stronger reactions, while the left forearm has had stronger reactions in 13 per cent of the total. Thus, the net predominance of the reactions in the right forearm was 2.3 per cent of the total series. A predominance of the reactions of the right forearm has been observed for two of the three used solutions, while in one solution, 1:100,000, the reverse was true.

The difference in the reactions of both forearms was, in most instances of this kind, quite considerable. In 4 per cent of the total the right

forearm has reacted while the left did not at all, and in 6.6 per cent of the total the left forearm has reacted while the right did not. In other words, in 10.6 per cent of the total, or in 32 instances, there has been observed an interesting phenomenon: the same dosage of the same solution of Old Tuberculin applied under the same conditions to both forearms has caused a positive reaction on one forearm and a negative on the other.

In the great majority of other cases of unequal reactions the difference between the reactions was one degree or more.

We were prompted by these rather unexpected findings to continue further the investigation of the regional skin hypersensitiveness. Two doses of 0.1 cc. of 1:1,000 solution of Old Tuberculin, taken from the same vial by the same special tuberculin syringe reserved for this solution only, were applied on two different areas of the anterior surface of the

TABLE 2

A study of the variation of skin hypersensitiveness to tuberculin on two different zones of the left forearm (100 individuals)

DILUTION	EQUAL REACTIONS ON BOTH FOREARMS	THE UPPER APPLICATION REACTED STRONGER			THE LOWER APPLICATION REACTED STRONGER			TOTAL OF ALL TESTS IN THE SERIES
		Total of tests in which both applications reacted	Upper applications reacted, lower did not	Total of all tests	Total of tests in which both applications reacted	Lower applications reacted, upper did not	Total of all tests	
		Number	Number	Number	Number	Number	Number	Number
1:1,000	53	10	2	12	32	3	35	100

left forearm, one on the upper third of the forearm, another about 8 cm. lower. One hundred persons were tested in this manner. The results of this series of tests are presented in detail in table 2.

Table 2 shows that in 5 per cent of the total the double testing of the same left forearm has given only one positive reaction. As in the previous series, the difference in the strength of the reactions was in the majority of the cases one degree or more.

DETERIORATION OF TUBERCULIN

It has been accepted by most workers that tuberculin solutions deteriorate considerably if kept for a long period of time, especially if exposed to heat, and consequently fail to produce positive reactions in subjects supposed to be tuberculin sensitive. The use of freshly prepared solutions, as the only reliable reagents, was therefore urged by many workers.

Such opinions are found in the older literature. According to Douglas and Hartley (1) such opinions were expressed by Jowett in 1914 and by Calmette in 1920. However, the newer literature contains facts tending to disprove this older conception. Pilcher (2) reports a marked stability of 1:10,000 solutions of Old Tuberculin kept on ice for a period of two years, 34 months and 39 months respectively. An ice-kept 1:1,000 solution of Old Tuberculin reacted after a four-year storage. Another vial of the same solution kept at room temperature for one and one-half years also retained its potency. Douglas and Hartley (1) report their findings on guinea pigs confirming Pilcher's data. According to these authors the solutions of tuberculin have retained not less than one-half of their potency after autoclaving and a prolonged heating at high temperatures. The same amount of stability has been retained on storage for 121 days at a temperature of 37°C. There was no loss of stability after a storage at room temperature for 53 days.

King (3) discussing the precautions which lead to the use of freshly prepared dilutions of tuberculin states, "It appears likely that tradition rather than fact, has been the basis of their adoption."

We have compared the potency of the freshly prepared and of the stock solution of Old Tuberculin. The former were prepared from Cutter's whole tuberculin. As a diluent we used the same one-half per cent solution of phenol in Baxter's distilled sterile water, fractionated and protein-free, which was used on one occasion in the previous series. Seven solutions of tuberculin were prepared of the following concentrations: 1:10, 1:100, 1:1,000, 1:10,000, 1:100,000, 1:1,000,000 and 1:10,000,000. They were, as a routine, discarded after one week's use, and fresh ones were prepared instead. Cutter's stock solutions of Old Tuberculin were used for comparison. They were kept on ice in different health centres of the Los Angeles County Health Department. Precautions were taken not to use solutions after the date of expiration printed on the label of the container. As stock solutions of lower concentrations, 1:1,000,000 and 1:10,000,000, were not available, we prepared them ourselves from Cutter's 1:100,000 solution using the above described diluent. These two solutions were not kept on ice, but carried around by us in the usual medical bag; they were each used for approximately six weeks. Five new tuberculin syringes were used for this series of tests for five consecutive solutions of Old Tuberculin starting with 1:10,000,000 and ending with 1:1,000, a separate syringe for each solution. As will be explained later, we did not find it necessary to use special syringes for the stronger

solutions of 1:100 and of 1:10. On testing, 0.1 cc. of the respective freshly prepared solution was injected intracutaneously in the patient's left forearm. The same dose of the respective stock solution was injected with the same syringe to the symmetric area of the right forearm. One hundred persons were tested with each of the following solutions: 1:10,000,000, 1:100,000, 1:10,000 and 1:1,000. Forty-six persons were tested with 1:1,000,000 solution; forty-four with 1:100; ten with 1:10. A total of 500 persons were tested in this series. Patients with active pulmonary tuberculosis, as more likely to react, were selected for the

TABLE 3

A study of the influence of deterioration of tuberculin on the degree of the intracutaneous reactions

DILUTION	EQUAL REACTIONS ON BOTH FOREARMS		THE FRESHLY PREPARED SOLUTION REACTED STRONGER						THE STOCK SOLUTION REACTED STRONGER						TOTAL OF ALL TESTS IN THE SERIES	
			Total of tests in which both solutions reacted		Freshly prepared solution reacted, stock solution did not		Total of all tests		Total of tests in which both solutions reacted		Stock solution reacted, freshly prepared did not		Total of all tests			
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
1:10,000,000	64	64	14	14	6	6	20	20	10	10	6	6	16	16	100	100
1:1,000,000	22	47.8	3	6.5	6	13	9	19.4	2	4.2	13	28.3	15	32.5	46	99.7
1:100,000	62	62	12	12	12	12	24	24	2	2	12	12	14	14	100	100
1:10,000	51	51	21	21	9	9	30	30	9	9	10	10	19	19	100	100
1:1,000	49	49	14	14	2	2	16	16	26	26	9	9	35	35	100	100
1:100	25	56.8	6	3.6	3	6.8	9	20.4	4	9.1	6	13.6	10	22.7	44	99.9
1:10	7	70	—	—	3	30	3	30	—	—	—	—	—	—	10	100
Total.....	280	56	70	14	41	8.2	111	22.2	53	10.6	56	11.2	109	21.8	500	100

tests with the weakest concentrations, up to 1:10,000; solutions of 1:10,000 and of 1:1,000 were used mostly on persons in whom active tuberculosis was not known to exist; the strongest concentrations of 1:100 and 1:10 were applied to persons who had yielded negative reactions to the previously applied weaker concentrations. The results of the tests are reported in detail in table 3.

In the majority of the tests there were equal reactions on both applications. The percentage of equal reactions for the total of the 500 tests was 56 per cent. The freshly prepared and the stock solutions have, on the whole, given a very close percentage of predominance in the strength of the provoked reactions. The greatest range of the pre-

dominance of the strength of the freshly prepared over the respective stock solution was manifested in the case of the 1:10 solution; the respective percentages in this instance were 30 and 0. However, in this particular instance the numbers of the tests reported were too small to be conclusive. In another instance, in which the numbers of the tests were large enough to be conclusive and in which the range in favor of the freshly prepared solution over the corresponding stock solution was the largest, in the 1:10,000 solution, the percentages were 30 and 19 respectively. In the instance of the 1:1,000 solution, the stock solution predominated in strength over the freshly prepared in 35 per cent of the tests, while the freshly prepared solution reacted more strongly in 16 per cent. However, for the total of the tests the freshly prepared solutions gave stronger reactions in 111 tests, or in 22.2 per cent; while the stock solutions gave stronger reactions in 109 tests, or in 21.8 per cent of the total. As can be seen, the figures for the total series show very convincingly that there has hardly been any difference at all in favor of one or the other solution.

Not wishing to encumber this paper with too many statistical data, we did not prepare either in this or in other series tables of comparison between the figures of the tests of this series with the respective figures of the variation in the skin hypersensitiveness on both arms which could serve as controls (table 1). We wish only to emphasize that in this series the reactions followed quite closely the same trend as the reactions of the skin hypersensitiveness series.

It would be noteworthy perhaps that in 41 instances, or in 8.2 per cent of the total, the freshly prepared solution reacted while the stock solution did not. In 56 instances, or in 11.2 per cent of the total, the stock solution reacted and the freshly prepared remained negative.

We wish to reiterate that 500 "double tests" have failed to bring out any differences at all in the reactive potency between freshly prepared and stock solutions of tuberculin. The variations observed in the reactions produced by each of the seven solutions used in this series are, in our opinion, due mostly to the variation of skin hypersensitiveness of both arms and perhaps only to a slight degree to the difference in potency of the solutions used.

"TENACITY" OF TUBERCULIN

Like many other biological preparations, tuberculin adheres with considerable tenacity to glassware. Parish and O'Brien (4) have reported

the results of different tests on guinea pigs mostly with undiluted tuberculin and also with various dilutions of tuberculin, including the weakest of 1:100,000. Repeated prolonged washings, in some instances after autoclaving, of the glass containers have failed to remove tuberculin completely, as invariably samples of washings injected subcutaneously have produced definite tuberculin reactions, in some instances of marked degree. Smith (5) describes a similar experience due to retention of tuberculin in a hypodermic needle previously used for tuberculin testing. Long (6) and associates have recently reported a series of intracutaneous tuberculin tests demonstrating the influence of "tenacity" of tuberculin on the outcome of the tests. Recently, findings based on the quantitative intracutaneous tuberculin (Mantoux) tests have been reported by many workers. It is obvious that, particularly in this kind of tuberculin test in which the limit of tuberculin sensitivity is to be determined for each individual, the accuracy of the test is likely to be jeopardized by the "tenacity" of tuberculin. We felt therefore that a more detailed investigation of this factor would be of interest.

In this series 0.1 cc. of stock solution of Old Tuberculin, taken from the same vial in each instance, was injected intracutaneously on the anterior surface of each forearm. "Special syringes," separate for each dilution, were used for the tests on the left forearm; another syringe routinely used for all tuberculin tests in the clinic, for the right forearm; in our further discussion it will be designated as the "clinic syringe." Dilutions of 1:10,000,000, 1:100,000, 1:10,000 and 1:1,000 were used in this series. One hundred individuals were tested with each of these dilutions, or a total of four hundred in this series. Findings are reported in detail in table 4.

Reactions of equal strength were noted in 201 instances, or in 50.2 per cent of the total. It is of interest that the percentage of equal reactions was the lowest in one of the weaker solutions (1:100,000), namely, 35 per cent, and that the curve of the percentages has shown a definite tendency to rise with the increase of the strength of the solutions, yielding 57 per cent for the 1:10,000 solution, and 68 per cent for the 1:1,000 solution.

Unequal reactions were observed in the rest of the tests. The reactions for which the "special" syringes were used were stronger than the reactions produced by the "clinic" syringes only in a small fraction of all cases.

The reactions produced by the "clinic" syringes were in many cases stronger than those for which the "special" syringes were used. The net prevalence of the strength of the reactions produced by the "clinic"

syringes was 35 per cent for the 1:10,000,000 solution, 47 per cent for the 1:100,000 solution, 23 per cent for the 1:10,000 solution, and 12 per cent for the 1:1,000 solution. It is to be noted that the curve of the percentages of the net prevalence of the strength of the reactions produced by the "clinic" syringes has, on the whole, had a tendency to descend from the peak reached by the reactions in which the 1:100,000 solution was applied to the lowest level for the reactions produced by the strongest solution used. The same tendency is observed when the absolute figures for the stronger reactions produced by the "clinic" syringes are studied. These curves are logically compatible with the curve of the percentages

TABLE 4

A study of the influence of "tenacity" of tuberculin on the degree of the intracutaneous reactions

DILUTION	EQUAL REACTIONS ON BOTH FOREARMS		THE TEST WITH THE CLINIC SYRINGE REACTED STRONGER						THE TEST WITH THE SPECIAL SYRINGE REACTED STRONGER						TOTAL OF ALL TESTS IN THIS SERIES	
			Total of tests in which both applications reacted		Tests with clinic syringe reacted; with special did not		Total of all tests		Total of tests in which both applications reacted		Tests with special syringe reacted; with the clinic syringe did not		Total of all tests			
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
1:10,000,000	41	41	32	32	15	15	47	47	8	8	4	4	12	12	100	100
1:100,000	35	35	21	21	35	35	56	56	5	5	4	4	9	9	100	100
1:10,000	57	57	12	12	22	22	34	34	3	3	6	6	9	9	100	100
1:1,000	68	68	16	16	6	6	22	22	6	6	4	4	10	10	100	100
Total.....	201	50.2	81	20.2	78	19.5	159	39.7	22	5.5	18	4.5	40	10	400	100

of the reactions of equal strength produced by both syringes. In 159 instances of the total series, or in 39.7 per cent, the "clinic" syringes have produced stronger reactions, while in 40 instances, or in 10 per cent, the "special" syringes have produced stronger reactions. The net prevalence of the strength of the reactions in which the "clinic" syringes have produced stronger reactions was equal to 29.7 per cent. Comparing these data with the corresponding data on the variation of specific skin hypersensitiveness on both forearms, used as control figures, (table 1) we recall that the net prevalence of the strength of the reactions on the right forearm was 2.3 per cent of the total series. In the present series the right forearm, on which the "clinic" syringes were used, has produced a net

prevalence of the strength of the reaction of 29.7 per cent. This comparison shows definitely that the difference in the reactions of this series was due to the "tenacity" of tuberculin and not other possible factors.

The possibilities of an error in testing, if the "clinic" syringes only are used, are clearly manifested after an analysis of the instances in which there was observed a positive tuberculin reaction on one forearm, while the other forearm remained negative (table 4). The tendency in the curve of the percentages described above was noted for this group of reactions also. The peak of the percentages of instances in which the "clinic" syringes have produced positive reactions while the "special" syringes have failed to produce any reactions at all was 35 per cent for the 1:100,000 solution; the percentage has descended to 22 for the 1:10,000 solution, and has reached the lowest level of 6 per cent for the 1:1,000 solution. The percentage of the instances in which the "special" syringes have produced positive reactions, while the "clinic" syringes have given negative reactions, has remained quite even and low, thus again repeating the tendency observed in the reactions produced by the "special" syringes in general. The net prevalence in this group of reactions produced by the "clinic" syringes over the same produced by the "special" syringes was equal to 15 per cent for the entire series. In other words, in one of every seven reactions the "clinic" syringes have produced positive reactions while the "special" syringes have produced negative reactions.

Comparing the corresponding figures for the 1:10,000,000 and 1:100,000 solutions, we note that the latter solution has yielded the highest percentage of instances in which the "clinic" syringes have reacted more strongly, thus being the only exception to the described tendency of the curves of the figures.

In our opinion, this occurrence could be due to the fact that the dose of 0.000,01 mgm. of Old Tuberculin placed in the "clinic" syringe at the time of the testing, and added to the residue of tuberculin remaining from the previous tests, is not potent enough to produce a definite reaction in certain subjects. The maximum of error was observed with the 1:100,000 dilution. Apparently, the larger dose of 0.001 mgm. of Old Tuberculin, together with the residual tuberculin remaining in the syringe, is the optimal dose for the production of the error. The decline of the degree of the error with the increase of the strength of the solution is apparently due to the fact that with the placing of consecutively increasing doses of tuberculin in the "clinic" syringe at the time of the testing, the possible influence of the residual tuberculin on the outcome of the reaction becomes

progressively smaller and reaches the lowest level with the strongest of the used solutions, 1:1,000. But even with this solution the net prevalence of the strength of the reactions produced by the "clinic" syringe over the same produced by the "special" syringe has been 12 per cent of this group. In other words, in our series the "tenacity" of tuberculin was a factor of an error even when the comparatively strong 1:1,000 solution was used.

The "tenacity" of tuberculin is undoubtedly a factor of clinical significance and its influence must be properly discounted in certain types of tuberculin tests.

THE SIZE OF THE WHEAL

Occasionally one finds in the literature references to the possible influence of the size of the wheal produced by the intracutaneous injection of tuberculin on the outcome of the ensuing reaction. Thus, Smith (5)

TABLE 5

A study of the influence of the size of the wheal produced by the injected tuberculin on the degree of the intracutaneous reactions

DILUTION	EQUAL REACTIONS ON BOTH APPLICATIONS	THE FOREARM ON WHICH THE 1:4000 SOLUTION WAS APPLIED REACTED STRONGER			THE FOREARM ON WHICH THE 1:1000 SOLUTION WAS APPLIED REACTED STRONGER			TOTAL OF ALL TESTS IN THE SERIES
		Total of tests in which both applications reacted	The forearm with 1:4000 solution reacted, other forearm did not	Total of all tests	Total of tests in which both applications reacted	The forearm with 1:1000 solution reacted, other forearm did not	Total of all tests	
	Number	Number	Number	Number	Number	Number	Number	Number
1:1,000	48	29	5	34	14	4	18	100

has found that with the stronger solutions, at least, the size of the reaction seems to depend more on the size of the wheal than on the actual amount of tuberculin injected. We have tested a group of 100 individuals for the determination of the possible influence of this factor. A dose of 0.1 cc. of 1:1,000 stock solution of Old Tuberculin was injected intracutaneously in the left forearm, and 0.4 cc. of 1:4,000 solution on the symmetric area of the right forearm. Thus, while the same dose of 0.1 mgm. was applied on both forearms, the volume of the solution injected on the right forearm was four times larger than that injected on the left forearm. At first, 0.2 cc. of 1:2,000 and 0.3 cc. of 1:3,000 solutions were tried but abandoned as they failed to produce a wheal noticeably differ-

ent in size from the one produced by the injection of 0.1 cc. of 1:1,000 solution in the left forearm. The same "special" syringe reserved for 1:1,000 solution was used for all tests in this series. The details of the findings are reported in table 5. The net prevalence of the strength of the reactions produced with the 1:4,000 solution over that produced with the 1:1,000 solution was 16 per cent. The control figure of the variation of specific skin hypersensitiveness for the tests in which the 1:1,000 solution was used on both forearms (table 1) yielded a net predominance of the strength of the reaction on the right forearm over the same on the left equal to 14 per cent.

Comparing the figures of 16 and 14 per cent, one may gain the impression that, at least in our series, the difference in the size of the wheal does

TABLE 6

A study of the influence of alcohol applied to the skin on the degree of the intracutaneous tuberculin reactions

DILUTION	EQUAL REACTIONS ON BOTH APPLICATIONS	THE WET FOREARM REACTED STRONGER			THE DRY FOREARM REACTED STRONGER			TOTAL OF ALL TESTS IN THE SERIES
		Total of tests in which both applications reacted	The wet forearm reacted; the dry did not	Total of all tests	Total of tests in which both applications reacted	The dry forearm reacted; the wet did not	Total of all tests	
	Number	Number	Number	Number	Number	Number	Number	Number
1:1,000	67	12	2	14	18	1	19	100

not influence appreciably the outcome of the reaction. However, the number of the tests in this series is not large enough to be definitely conclusive.

THE INFLUENCE OF ALCOHOL

Some authors describing the technique of the intracutaneous tuberculin (Mantoux) test stress the necessity of drying the alcohol usually applied before the injection of tuberculin. We have attempted to investigate whether alcohol would influence the result of the reaction thus justifying a thorough drying. A group of 100 individuals was used for this purpose. Alcohol used for washing of the skin of the forearms was thoroughly dried on the left forearm, while the right forearm remained wet with alcohol. An equal dose of 0.1 cc. of 1:1,000 solution of Old Tuberculin, taken in each instance from the same vial, was applied on the anterior surface of each forearm. The same "special" syringe re-

served for 1:1,000 solution was used in this series. The findings are reported in table 6. The net prevalence of the strength of the reaction on the left dry forearm over the same on the right wet was 5 per cent. Comparing this figure with the control figure for 1:1,000 solution (table 1) in which, as has been mentioned, the net prevalence was in favor of the right forearm to the extent of 14 per cent, one may get the impression that perhaps in certain cases alcohol may suppress specific skin hypersensitiveness to some extent. However, the number of the tests in this series is too small to render this conclusion acceptable.

DISCUSSION

As has been mentioned before, the skin tests were read by the nurses of the Los Angeles County Health Department. Though test readings by different persons are naturally bound to differ to a certain extent, due to the difference in individual interpretations, we feel that this factor could not influence noticeably the reported results. The readings were always comparative of two simultaneously applied reactions and, if a certain degree of individual difference or even an error in interpretation would be committed, the readings of both tests would be equally affected and, thus, the net prevalence of one test over the other would still be expressed correctly.

This investigation brought out facts which seemingly point to the difference in the regional skin hypersensitiveness in a certain quite large group of cases. This is by no means a phenomenon peculiar to tuberculin. There are convincing reports by different investigators stressing this variability of sensitivity of different skin zones to certain allergens. In another series of quantitative tuberculin tests, the result of which we hope to report later, we observed that on some occasions the difference of the tuberculin reactions on both forearms was quite considerable. We observed quite a few instances in which one arm reacted to a certain dose of Old Tuberculin while the other, on which a ten times stronger dose was applied, remained negative. However, it was possible to elicit finally a positive tuberculin reaction by consecutive increases of the applied dose. Comparing the sensitivity of both forearms, one feels that though the corresponding figures have markedly differed with different solutions, the average findings for the total series of 300 tests could hardly have lead to the conclusion that one forearm is as a rule more sensitive to tuberculin. On the contrary, it seems that the lower portion of the anterior surface of the left forearm is more tuberculin sensitive than

the upper portion. Of course, a much larger number of tests must be studied to arrive at definite conclusions. Nevertheless, it appears on the basis of the reported observations that this factor of the regional variation of skin hypersensitiveness has a definite practical significance. We feel that in order to avoid its misleading effect in tuberculin testing, consecutively increasing doses of Old Tuberculin, including if necessary 10.0 mgm., should be applied in the cases with negative reaction to lower doses.

We also feel that this factor ought to be taken into consideration when comparative studies of the potency of different tuberculins are made as, for instance, the repeatedly reported investigations of PPD.

In the series in which deterioration of tuberculin was studied, the freshly prepared solutions of tuberculin were compared with different stock solutions routinely used in several different health centres of the Los Angeles County Health Department. One must bear in mind that, though released by the same manufacturer, different vials may contain solutions of Old Tuberculin prepared from different batches and therefore varying in potency. The same difference of potency, due to the same factor, could also be expected to exist between various vials of stock tuberculin solutions and the solutions freshly prepared by us. A point of criticism of our findings could be made on this basis. However, we have deliberately selected the reported technique of comparative testing, as our object was to ascertain whether the different solutions of Old Tuberculin would be noticeably affected in potency by the manner in which they are being kept in different health centres. It was not our aim to embark upon a study of the factor of deterioration of tuberculin in general.

The newer literature does not deny the fact of the partial loss of potency of tuberculin through deterioration which was strongly stressed by the older authors. But it is the impression of the recent workers that this loss of potency is not sufficient to be of practical significance. This impression seems to be confirmed by the results of our series of 500 tests. It seems that properly kept on ice and used before the date of expiration stated on the label of the container, the stock tuberculin solutions could be safely relied on. However, we wish to emphasize that this conclusion resulting from the observations on tests made with one make of Old Tuberculin may or may not apply to other makes.

The curves of changes in the reactions due to "tenacity" of tuberculin discussed in the earlier part of the paper seem to confirm the observations

of other workers as to the practical significance of this factor. Its distorting influence must be seriously taken into consideration in quantitative tuberculin testing. As we have seen, the application of smaller doses of tuberculin, which are so essential in estimating the lower limit of tuberculin sensitivity, is especially affected by the "tenacity" of tuberculin. However, this factor is of no practical significance for qualitative testing for absence or presence of tuberculin sensitivity.

The factors of the difference of the size in the wheal produced by the injected tuberculin and of the alcohol applied to the site of the injection and their possible influence on the outcome of the reactions were sufficiently discussed previously.

We wish to state that we anticipate a possibility that repeated with a much larger number of tests this investigation could result in somewhat different conclusions; we feel that the conclusions reported here are acceptable only as valid for the number of tests used by us. We also feel that our findings, though of significance for a group or a series of tests as made and observed by us, are not necessarily applicable to each and every individual tuberculin test, due to the fact that many factors, some of them not completely known as yet, may influence the outcome of individual tests.

SUMMARY AND CONCLUSIONS

1. A series of 400 "double" tests has demonstrated that the regional variation of specific skin hypersensitiveness to tuberculin is a factor of a practical significance.

2. A series of 500 "double" tests has yielded results seemingly indicating that the deterioration of tuberculin does not affect its potency to a degree definitely distorting the outcome of the intracutaneous reaction.

3. A series of 400 "double" tests has revealed that the "tenacity" of tuberculin undoubtedly exerts a distorting effect on the result of the intracutaneous reaction, depicted in our series by a curve which reached its peak when the 1:100,000 solution of Old Tuberculin was used and which came down to its lower levels with the increase of the concentration of the solutions of Old Tuberculin.

4. A series of 100 "double" tests has apparently failed to demonstrate a noticeable effect of the size of the wheal produced by the injected tuberculin on the size of the reacting skin area.

5. A series of 100 "double" tests has given results suggesting a prob-

able somewhat retarding effect of alcohol on the intracutaneous tuberculin reaction.

We wish to express our thanks to Dr. J. L. Pomeroy, Los Angeles County Health Officer, for his permission to publish this report; to Dr. P. K. Telford, Chief of the Tuberculosis Division, for his interest and coöperation in this work; and to the nurses of the Department for their efforts in careful reading of 3,000 tests made during this investigation.

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THE INCIDENCE OF TUBERCULOSIS AMONG BLIND SCHOOL CHILDREN[1]

CAMILLE KERESZTURI

During the school year 1936–1937 the New York Institute for the Education of the Blind undertook an extensive health program, part of which consisted of the examination of the pupils for tuberculosis.[2] When this part of the study was finished, we wished to compare the incidence of tuberculosis among our blind children with the incidence of the disease in other institutions of similar nature. We were unable to find any article in the available medical literature concerning tuberculosis among the blind. It seems worth while to us, therefore, to report the findings of our study.

There is, of course, an abundant literature concerning the incidence of tuberculosis among normal school children at various age levels in many localities. When one wishes to compare one's findings with the results of others, it is important to keep in mind the following facts:

1. The incidence of tuberculous infection increases as children get older.
2. It seems to be higher if tests with larger doses of tuberculin are used.
3. It varies from one community to another and is lower among rural children.
4. It varies among different races.
5. It is lower among children of well-to-do families who do not live in congested tenements.
6. It is higher among children with tuberculosis in their families.
7. The incidence of tuberculous infection among the general population is on the decline.

Considering all these factors which influence the apparent incidence of tuberculous infection, it is obvious that it is hard to compare our findings with the results of other investigators, who have studied the same problem among normal school children. One should choose a

[1] From the Department of Diseases of Children, Columbia University, New York City.

[2] This study was made possible through the interested coöperation of Dr. William Barcley Parsons, one of the trustees of the New York Institute for the Education of the Blind; of Dr. Merle E. Frampton, the Principal; and of Mrs. K. D. Longsdorf, R.N., the nurse of the school.

report dealing with children of the same age, of the same racial composition, in the same economic status, with the same exposure to tuberculosis, in the same city about the same time. Since no such study is available, our data cannot be accurately matched with other studies, and the comparisons offered hereafter should be considered to be only approximately correct.

The Institute for the Education of the Blind is a State school with private endowment for the education of partially and completely blind children from the age of 5 to about 22 years. It is a combination of day school and boarding school, but this year only 6 of the 200 pupils went home every night. The rest left the Institute only on weekends. Seventy-five per cent of the pupils are residents of New York City. The school is not in session for two months in the summer. The pupils pay no tuition. Most of the families from which they come are in the class of the parents whose children go to public schools; a few, however, could afford private schooling for their children. As a whole, the school population closely resembles that of a public school in a fairly good neighborhood in New York City. At the time of the present survey 200 pupils were registered in the school. Two of the children were absent during the period of investigation and were not included in this report.

The ages of the pupils ranged from $5\frac{1}{2}$ to 22 years. The mean age was 13.9 years, with a standard deviation of 4.1. This means that about 68 per cent of the children fell between the age limits of 9.8 and 18 years.

The procedure chosen for our study was the following: All the children were tuberculin-tested intracutaneously by the Mantoux method with 0.01 mgm. Old Tuberculin. If the reaction was not unquestionably positive, a second tuberculin test with 1.0 mgm. OT was done. All the positive reactors were examined clinically and roentgenograms of their chests were made, their sputum was examined for tubercle bacilli by smear and by culture, and their erythrocyte sedimentation rates and their diurnal temperatures at four-hour intervals were determined.

TUBERCULIN TESTS

As may be seen from table 1, 198 children received an intracutaneous tuberculin test with 0.01 mgm. OT. Only 22, or 11 per cent, of them gave an unquestionably positive reaction. Of the remaining 176, 134 reacted entirely negatively to this smaller dose; but 14, or 10 per cent, of these gave a definitely positive reaction to the one hundred times stronger

dose of 1.0 mgm. Forty-two of the original 198 subjects gave a suspicious reaction to 0.01 mgm. OT, but 31 of these, or 74 per cent, became definitely positive when 1.0 mgm. OT was used. In other words, of the 198 children tested either with 0.01 mgm. or with this dose and afterward with 1.0 mgm. OT, 67, or 34 per cent, reacted positively. Throughout this study, the standards of Aronson (1) were used for the definition of positive and negative tuberculin reactions.

Among the 198 children originally tested with 0.01 mgm. OT, none showed constitutional reactions, and only one showed local reaction with formation of a vesicle. Of the 134 entirely negative reactors to 0.01 mgm. OT, 14, or 10 per cent, reacted positively forty-eight hours later when tested with 1.0 mgm. Of the 42 children who reacted doubtfully to the smaller dose of OT, however, 31, or 74 per cent, became unques-

TABLE 1

Tuberculin tests among blind children

DESCRIPTION OF TESTS	TOTAL NUMBER OF TESTS	NEGATIVE OR DOUBTFUL	POSITIVE	PER CENT POSITIVE
Initial intracutaneous with 0.01 mgm. OT	198	176	22	11
Retest with 1.0 mgm. OT after negative result with 0.01 mgm	134	120	14	10
Retest with 1.0 mgm. OT after doubtful result with 0.01 mgm	42	11	31	74
0.01 mgm. OT and if negative or doubtful 1.0 mgm. OT	198		67	34

tionably positive when tested with the larger dose. Only one of the 176 children tested with 1.0 mgm. OT showed severe local reaction with vesiculation, and 12, or less than 7 per cent, showed constitutional reactions. All of these twelve, except one, had also shown questionably positive local reactions to the original test; they were among the 42 doubtful reactors to the 0.01 mgm. OT dose. The consitutional reactions were very mild, consisting of headaches, malaise, slight fever, and regional lymphadenitis for one to two days.

Judging from the outcome of our tests, we feel that 0.01 mgm. OT is a suitable initial dose. On questionably positive subjects the second test had better be made with 0.1 mgm. OT rather than with 1.0 mgm., in order to avoid unpleasant and unnecessary constitutional reactions, amounting in our series to 7 per cent.

Not all investigators have found entirely consistent results in tests of

this type. Hart (2), for example, states that upon increasing the tuberculin test dose from 0.01 mgm. to 10.0 mgm., 4 per cent additional positive reactors are found; but Barnard, Amberson and Loew (3) found 15 per cent more positive reactors when they used 1.0 mgm. OT than when they used 0.1 mgm. for the Mantoux tests. Our experience was that increasing the test dose from 0.01 mgm. OT to 1.0 mgm. on definitely negative reactors disclosed 10 per cent more positive cases. But when questionably positive reactors to 0.01 mgm. OT were retested with 1.0 mgm., 74 per cent of them became definitely positive. If one wishes to discover all the positive reactors, therefore, it seems worth while to increase the tuberculin test dose to 1.0 mgm.

Our total of 34 per cent positive reactors out of the original 198 tested is considerably lower than the 67 per cent which Barnard, Amberson and Loew (3) found in a group of 1,000 white school children in the Bellevue-Yorkville district of New York City. The age distribution of their group was 12 to 15 years, and the OT dosage 0.1 to 1.0 mgm. On the other hand, no significant difference is apparent between our present findings and those obtained with 7,668 cases at Bellevue by Smith (4), or with 1,605 children tested by us at the former Fifth Avenue Hospital (5), or with the 14,699 children and infants reported by Drolet (6).

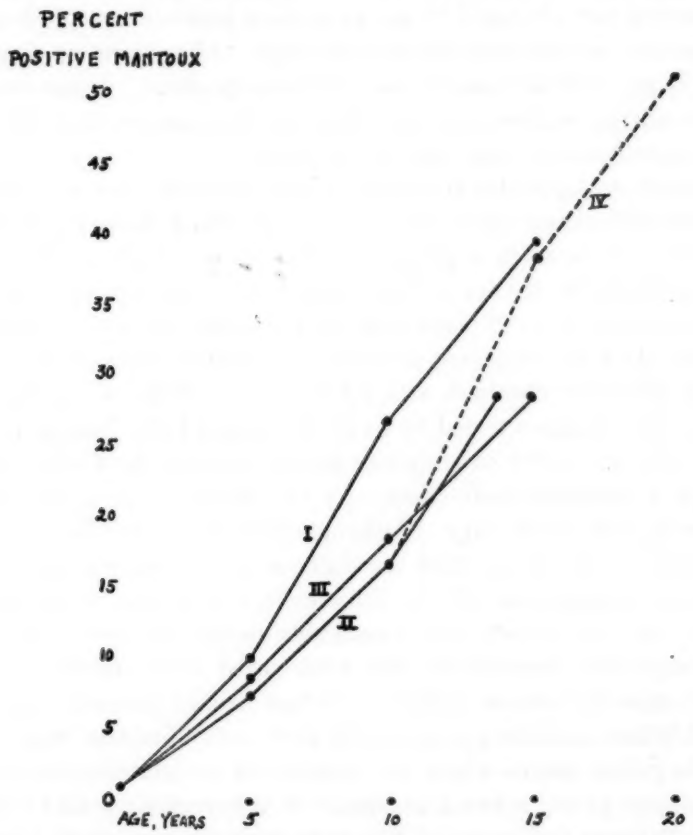
Graph 1 compares four surveys of the incidence of tuberculosis of children in New York City. Although there is a difference of 5 to 16 years between the dates when the different groups were tested, and although the testing dose of Old Tuberculin also varied in the different surveys, the four curves run remarkably nearly parallel. This result was unexpected, because we had anticipated lower figures for blind children than for normal children. It had seemed probable that, since blind children would be prevented by their very blindness from moving freely in public places where the chances of extrafamilial tuberculous infection are great, a lower incidence of tuberculosis would naturally occur. Perhaps the factor of lesser exposure was counterbalanced by closer confinement of the blind in smaller places with one another and with the members of their own families. Whatever the explanation may be, the fact is clear that the incidence of infection with tuberculosis in this group of blind children in New York City is the same as among children with normal vision.

One might object, perhaps, that it is not fair to compare statistics from hospitals and from schools. Drolet (6), however, did not find any significant difference in the incidence of tuberculous infection between

subjects in well-baby clinics and those in hospitals. On the assumption that his findings are accurately representative, it seems fair, then, to compare statistics from schools and from general hospitals.

GRAPH 1

Incidence of tuberculosis infection in various groups of children in New York City



I, Bellevue, 1921–1928, 0.05–2.0 mgm. OT.
II, Fifth Avenue Hospital, 1930–1931, 0.1 mgm. OT.
III, Drolet, 1930–1932, 0.01–1.0 mgm. OT.
IV, Blind Children, 1937, 0.01–1.0 mgm. OT.

Of the 200 pupils at the school, 122 were males and 78 females. Forty per cent of the boys were positive reactors. Of the 76 girls, 22 per cent were positive. Most authors have found no significant difference between the incidence of tuberculous infection in boys and girls.

As may be seen from table 2, Americans (27 per cent) and Italians (18 per cent) predominated in the population of the Institute, and totaled approximately half the group. Negroes made up another 10 per cent,

TABLE 2

Race and nationality distribution of pupils of the New York Institute for the Education of the Blind

	per cent
American	27
Italian	18
Negro	10
Jewish	9
Russian	5
Irish	4
German	3
Others	10
Mixed nationalities	14
	100

TABLE 3

Comparison of different forms of abnormal shadows in the roentgenograms of tuberculin-positive children

NATURE OF SHADOW	BARNARD AND AMBERSON'S SERIES		OUR SERIES	
	Number	Per cent	Number	Per cent
In lung parenchyma	26	14	3	20
Enlarged tracheobronchial shadow	89	49	8	53
Primary complexes	69	37	3	20
Thickened pleura	0		1	7
All Mantoux-positive cases with abnormal chest roentgenograms	184 out of 670*	29	15 out of 67	22
Clinically significant shadows in tuberculin-positive group	15 out of 184	8	3 out of 67	4
Clinically significant shadows in entire group	15 out of 1000	1.5	3 out of 198	1.5

* 13, or 7 per cent, of these were tuberculin-negative.

and Jews 9 per cent. The figures in this table are based on information about the birthplaces of the parents.

We do not believe that there is enough difference in the incidence of tuberculous infection among different races to justify a comparative

analysis of our small series and other New York groups from the point of view of race and nationality.

Two, or 1.5 per cent, of the 131 tuberculin-negative children were exposed to known tuberculosis in their homes. Five, or 7 per cent, of the tuberculin-positive subjects were similarly exposed. Among the children who showed abnormal roentgenographic shadows suggesting pulmonary or mediastinal involvement, the incidence of known exposure to tuberculosis was 2 out of 15, or 13 per cent. In Barnard, Amberson and Loew's series (3), 9 per cent of the patients with abnormal roentgenograms were known to have been exposed to intrafamilial tuberculosis.

ROENTGENOGRAMS OF THE CHEST[3]

The thoraces of all the positive reactors to Old Tuberculin were examined roentgenographically in the posteroanterior direction. Fifteen of the 67 cases, or 22 per cent, showed abnormal shadows. Only 3 of the 15, however, or 4 per cent of the 67, had what we interpreted as clinically significant shadows. In other words, 3 patients, or 1.5 per cent of the entire group of 198 children examined, showed clinically significant shadows. This figure is within the limits of expected clinical tuberculosis in the average New York City school population, and is identical with the ratio of manifest tuberculosis found by Barnard, Amberson and Loew (3) in their study of 1,000 unselected school children.

It is noteworthy that 12 of our 15 subjects who showed abnormal roentgenographic shadows in the chest were boys. Of the 3 patients with what we considered clinically significant lesions, 2 were males and 1 female. Barnard, Amberson and Loew (3) also found that more boys than girls showed abnormal roentgenograms. Our roentgenographic results were in all respects closely similar to those of Barnard, Amberson and Loew.

SUBJECTIVE COMPLAINTS AND PHYSICAL EXAMINATION

Three of the 15 roentgenographically positive children showed a stationary weight curve. One child had slight cough, and one showed a temperature up to 100.2°F. None of the children had any expectoration, and only one of them was obviously malnourished. Only one of the patients who showed abnormal roentgen shadows had occasional râles in one of the apices after cough. A roentgenogram of this patient showed

[3] Read by Dr. John Coffey of Babies Hospital, New York City.

bilateral apical changes. The other 14 cases were all normal on careful physical examination.

EXAMINATION OF THE SPUTUM

As only one of the children manifested any cough, we attempted to obtain specimens of sputa by training patients to cough forcibly and repeatedly. Twelve of the 15 roentgen-positive patients could produce satisfactory specimens of sputum for study. None of the sputa showed tubercle bacilli, either by smear or by culture. The examination of gastric content of our children could not be carried out in this school survey.

TABLE 4

Erythrocyte sedimentation rates (one hour values) on patients with positive Mantoux tests and pathological roentgenograms

RATE IN 1 HOUR *	NUMBER OF CASES	TYPE OF CASES
Less than 10 mm.	6	4 Tracheobronchial shadows 2 Parenchymal shadows
10–20 mm.	7	3 Tracheobronchial shadows 3 Primary complexes 1 Thickened pleura
20–30 mm.	1	1 Peribronchial lymph node enlargement
30–40 mm.	1	1 Parenchymal shadow

* Modified Westergren technique used; normal values are below 15 mm. per hour.

ERYTHROCYTE SEDIMENTATION RATES

As table 4 indicates, 13 of the ESR values among the 15 children who had a positive tuberculin test and some abnormal shadow in roentgenograms of the chest were within normal limits. One of the children who showed calcified peribronchial shadows had an ESR of 27 mm. in one hour. The highest ESR value, 38 mm. in an hour, occurred in one of the three children who showed clinically significant parenchymal shadows.

CAUSES OF BLINDNESS

Judging by the fact that the incidence of tuberculous infection in our group was not higher than in similar groups of children in New York City having good vision, we can assume that tuberculosis was not often

the cause of blindness among the pupils of the New York Institute for the Education of the Blind.

Table 5, prepared by the Committee on Statistics of the Blind, shows the various known causes of blindness among the pupils of the New York Institute for the Education of the Blind and in 27 other similar institutions. Since tuberculosis as an aetiological factor is not separately listed, it may be assumed that it occupies an insignificant place among the causes of partial or complete loss of sight.

TABLE 5*

Summary of statistics on causes of blindness

New York Institute for the Education of the Blind and 27 other schools and classes for blind

ALL CAUSES—ETIOLOGICAL	NEW YORK INSTITUTE FOR THE EDUCATION OF THE BLIND	27 OTHER SCHOOLS AND CLASSES FOR THE BLIND
	percentage	*percentage*
1. Infectious diseases:		
a. Measles	1.2	1.1
b. Meningitis	3.1	1.8
c. Ophthalmia neonatorum (gonorrhoeal)	12.0	12.1
d. Syphilis	3.1	4.6
e. Others not specified	8.0	10.1
Total, infectious diseases	28.3	29.7
2. Traumatic and chemical injuries	9.8	8.1
3. Toxic poisoning	0.0	0.1
4. Noninfectious systemic diseases	3.1	1.2
5. Neoplasms	2.5	2.1
6. Congenital and hereditary	53.2	48.3
7. Aetiology not specified	3.1	10.5

* Prepared by the Committee on Statistics among the Blind.

DISPOSITION OF CASES

In our survey in the New York Institute for the Education of the Blind, we found, among the 198 children examined, 52 who showed tuberculous infection without evidence of clinical disease. Twelve children showed arrested pulmonary tuberculosis of childhood type which did not require treatment. Three pupils manifested the adult type of pulmonary tuberculosis with mild clinical significance. It was advised that two of these latter children be observed at home and in school, and that the third be sent to a sanatorium for tuberculosis.

SUMMARY AND CONCLUSIONS

1. A survey was made of the incidence of tuberculosis among 198 completely or partially blind school children ranging in age from 5 to 22 years.

2. The frequency of tuberculous infection as determined by 0.01 to 1.0 mgm. Old Tuberculin intracutaneously was 34 per cent, or about the same as in school children of similar age but with good vision, living in New York City.

3. The incidence of pathological roentgenographic changes in the tuberculin-positive group was 22 per cent, and the incidence of clinically significant shadows in the same group was 4 per cent.

4. If we express the incidence of our positive roentgenological findings in terms of the entire group of 198 children examined, we find 7.5 per cent of the total number showing abnormal shadows, and one-fifth of these, or 1.5 per cent of the whole group of 198, showing shadows of apparent clinical significance.

5. None of the children who showed abnormal roentgenological shadows had a positive sputum by either smear or culture.

6. As a result of our survey among 198 blind children at the New York Institute for the Education of the Blind, 67, or 34 per cent, have been diagnosed as being infected with tuberculosis. Of this number, 15 showed roentgenological evidence of the disease in the lungs. Twelve of these 15 showed an apparently arrested childhood type of tuberculosis and 3, probably, an adult type of the disease. Only one child needed sanatorium care, and two others careful observation and periodic examinations.

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TUBERCULOSIS SURVEY IN CHICAGO HIGH SCHOOLS[1]

J. B. NOVAK AND J. S. KRUGLICK

In January of 1933, the Chicago Tuberculosis Institute began a tuberculosis survey in the Chicago high schools. This survey was completed early in 1937. During this time some 26,000 students were examined for tuberculosis. We wish here to present the findings of this survey and the impressions created upon us by this work.

In outlining this project we will present: (*a*) the plan of the work; (*b*) the skin-testing results with the various tests, materials and dilutions used; (*c*) a comparative study in one group who were reëxamined after twelve to eighteen months; and in conclusion (*d*) a follow-up study of all definite and suspicious cases disclosed in the first three years of the survey.

The plan of the work was to go into the school and present at a series of student assemblies a simple but thorough explanation of the examinations to be made. An instructive sound film on tuberculosis was shown and an explanatory lecture was given on the tuberculin test. The significance of positive and negative reactions was made clear.

All students were then given consent slips to be signed by their parents. Those that returned signed slips were given the tuberculin test. All positive reactors were X-rayed and all those with suspicious X-rays were given physical examinations. In addition, wherever it was deemed necessary, sputum examinations were made. In this manner the status of each student was determined and the parents advised by mail.

In every definite or suspicious case found, home calls were made by our nurse. The possibility of contact in the home was thus sought out and the family further advised. The nurse continued to make calls upon these individuals until it was assured that they and the members of the family were in competent hands for further observation and care.

We wish to present the statistics in the Chicago area for some 26,000 students who were given the tuberculin test. The last figures found in the literature for this city were presented in 1932 by Webb (1), with a considerably smaller group.

[1] From the Chicago Tuberculosis Institute, Chicago, Illinois.

In the first year of the testing, 1933, the Pirquet test was used exclusively; 4,737 white and 1,671 Negro children, ranging in age from 13 to 20 years, were tested. The percentage of positive reactions for the whole group was 35.67. The Negro children ranged about 2 per cent higher than the white children. Table 1 gives the figures for the various age groups.

It was our feeling, after one year and 6,000 tests with the Pirquet method, that even to the experienced individual there was some difficulty in uniformity of technique and interpretation. For this reason it was abandoned in favor of the Mantoux test.

TABLE 1

Results of Pirquet tests according to age and race

AGE	WHITE			NEGRO			TOTALS		
	Number tested	Number positive	Per cent positive	Number tested	Number positive	Per cent positive	Number tested	Number positive	Per cent positive
years									
12 and 13	46	13	28.26	32	10	31.25	78	23	30
14	253	154	60.86	156	56	35.89	409	210	51.34
15	1,238	411	33.19	345	122	35.36	1,583	533	33.67
16	1,536	555	36.13	400	155	38.75	1,936	710	36.66
17	1,080	347	31.11	346	142	41.04	1,426	489	34.35
18	426	134	31.45	219	65	30.00	645	199	30.85
19	120	44	36.66	121	47	38.91	241	91	37.75
20	25	7	28	40	14	35.00	65	21	32.30
21	9	2	22.2	9	5	55.55	18	7	39
22	4	0	0	3	3	100	7	3	42 plus
Total.....	4,737	1,667	35.18	1,671	619	37.04	6,408	2,286	35.67

It may seem superfluous to bring up at this time a controversy regarding the Pirquet test since it has practically been abandoned in group testing in this country. We feel, however, that it is still enjoying vogue with the general practitioner as we are often called upon to aid in interpretation. It is also being used considerably in foreign countries.

Our own figures reveal the Pirquet test giving a slightly higher percentage of positive reactors than the Mantoux test (using a single dose of 0.1 mgm. of OT). Despite this difference we urge the abandoning of the Pirquet test in favor of the Mantoux test. The latter, we feel, is more uniform, more accurate, and more rapidly done. A comparison of tables 1 and 2 will disclose the expected uniform increase with age in the Mantoux group and the irregularity in the Pirquet group.

In conclusion it may be said that for speed of performance, for ease of interpretation, and for accuracy and uniformity of results, the Pirquet test should be abandoned in favor of the Mantoux test.

During the next two years (1934 and 1935) the Mantoux test, using OT 0.1 mgm., was done. A single test was used; 10,747 white children were tested with 26.15 per cent positive, and 1,764 Negro children were tested with 34.81 per cent positive. Table 2 shows the results.

Drolet (6) found no difference in the incidence of infection in boys and girls of ages one to fifteen. Long and Seibert (7) found, in a group entering college, a higher rate of infection in men than in women. In our own group, an intermediate group, thirteen to seventeen years of age, we

TABLE 2

Results of Mantoux tests with 0.1 mgm. OT according to age and race

AGE	WHITE			NEGRO			TOTALS		
	Number tested	Number positive	Per cent positive	Number tested	Number positive	Per cent positive	Number tested	Number positive	Per cent positive
years									
12 and 13	522	124	23.73	89	25	28.08	611	149	24.38
14	2,199	536	24.37	291	86	29.55	2,490	622	24.99
15	3,113	755	24.25	341	108	31.67	3,454	863	25.00
16	2,784	747	26.83	439	152	34.65	3,223	899	27.89
17	1,524	445	29.20	327	118	36.08	1,969	563	28.60
18	478	158	33.05	186	82	44.06	664	240	36.14
19	102	38	37.25	72	37	50.13	174	75	43.10
20	15	6	40.00	14	4	35.00	29	10	34.48
21	1	1	100	5	2	40.00	6	3	50
22	9	1	11.11	0	0		9	1	11.11
Total.....	10,747	2,811	26.15	1,764	614	34.81	12,511	3,425	27.37

found no difference in the incidence of infection in the sexes. Therefore, no sex segregations were made in our charts.

In 1936 we began using two tests; 5,089 white students were given two tests with PPD, with 50.83 per cent positive; 2,485 Negro students were tested, with 69.69 per cent positive. The large difference between white and Negro students lies in the first test; with the second test in both groups, the increase was about 20 per cent.

Table 3 shows the results obtained with PPD. Here again the uniform increase with age will be noted.

A group of 870 white and Negro students was tested with two tests, using OT 0.1 mgm. and 1 mgm. With the first test, 33.9 per cent reacted; with both tests 58.16 per cent reacted positively (table 4).

Table 5 shows a comparison of the various materials and tests used. From this table it can be seen that there is little to choose in percentage of positive reactors between OT and PPD. It would seem, then, that the important points to observe in a skin-testing project are the use of fresh material (OT or PPD) and the use of two tests.

TABLE 3

Results of Mantoux tests with first and second strength PPD

AGE	WHITE							NEGRO						
	Number tested	Positive						Number tested	Positive					
		First strength		Second strength		Both tests			First strength		Second strength		Both tests	
years			*per cent*		*per cent*		*per cent*			*per cent*		*per cent*		*per cent*
12 and 13	212	64	30.18	25	11.72	89	41.9	129	45	34.88	19	14.73	64	49.61
14	978	306	31.29	150	15.33	456	46.62	428	179	41.82	84	19.62	263	61.44
15	1,500	448	29.2	305	21.00	753	50.2	668	305	45.65	147	22.01	452	67.66
16	1,198	340	28.38	278	23.22	618	51.6	684	343	51.6	159	21.79	502	73.39
17	784	247	31.37	174	22.33	421	53.7	361	186	51.52	93	25.76	279	77.28
18	332	113	34.03	84	24.27	197	59.3	162	94	58.02	38	23.39	132	81.41
19	56	21	37.5	13	23.2	34	60.7	45	27	60.00	8	17.77	35	77.77
20	19	8	42.11	4	21.04	12	63.15	5	2	40	1	20.00	3	60.00
21	7	3	42.85	3	42.85	6	85.7	1	1	100	0	0	1	100
22	3	1	33.3		0	1	33.3	2	1	50.00	0	0	1	50
Total	5,089	1,551	30.47	1,036	20.36	2,587	50.83	2,485	1,183	47.64	549	22.05	1,732	69.69

TABLE 4

Results of Mantoux test with OT, 0.1 and 1.0 mgm.

NUMBER TESTED	POSITIVE, 0.1 MGM.	POSITIVE, 1.0 MGM.	TOTAL POSITIVE
870	295 33.90 per cent	211 24.26 per cent	506 58.16 per cent

Long and Seibert (12) feel that all patients who react to two tests would react were the second strength alone used. We believe that the use of two tests is important and that often the first test causes a reawakening of the allergy or an anamnestic reaction. We are at present completing a piece of work which appears to prove this contention and will be published at a later date.

Table 6 is a compilation of all the work done, showing the results of the X-ray and physical examinations. It is interesting to note that in no

instance was a case of tuberculosis found among the group who reacted only to the second strength. There was in this group only one suspicious

TABLE 5

A compilation of all the skin testing

MATERIAL AND TEST USED	NUMBER TESTED	NUMBER POSITIVE			PER CENT POSITIVE		
Pirquet single test	6,408	2,286			35.67		
Mantoux test with 0.1 mgm. OT	12,511	3,425			27.37		
		1ST	PER CENT	2ND	PER CENT	BOTH	PER CENT
Mantoux test with PPD, two tests	7,574	2,734	36.09	1,585	20.93	4,319	57.02
Mantoux test with OT, 0.1 and 1.0 mgm	870	295	33.9	211	24.26	506	58.16

TABLE 6

Physical and X-ray findings

TUBERCULIN TEST	NUMBER TESTED	NUMBER POSITIVE	PER CENT POSITIVE	X-RAYED	PHYSICAL EXAMINATION	PULMONARY TUBERCULOSIS	TUBERCULOSIS SUSPECTED	HEALED CHILDHOOD-TYPE TUBERCULOSIS	NORMAL	REMARKS
Pirquet	6,408	2,286	35.67	2,185	242	11 (.5%)	6 (.26%)	449 (20.55)	1,719 (78.68)	
0.1 mgm. OT, intracutaneous	12,511	3,425	27.37	2,717	121	13 (.47%)	29 (1.06)	605 (22.23)	2,070 (76.18)	8 arrested cases and 1 bone tuberculosis
PPD, 2 tests	7,574	4,319	57.02	3,883	162	22 (.56%)	24 (.61%)	610 (15.7)	3,190 (83.13)	37 observation cases
OT, 0.1 and 1.0 mgm. intracutaneous	870	506	58.16	485	21	4 (.82%)	0	108	373	

case. These findings agree essentially with findings of other observers, such as Long and Seibert (12).

In two groups there was a retesting of the negative reactors within a period of 12 to 18 months. In one of these groups 1,018 students (all white) were retested. OT 0.1 mgm., a single dose, was used for the original testing and the retesting. In this group 49 children, or 4.81 per cent, changed in skin reaction from negative to positive. Two students who had changed in reaction from negative to positive showed definite incipient tuberculosis.

In the second group, consisting of 404 students (70 per cent Negroes), the original testing had been done with a single dose of OT 0.1 mgm. The retesting was done with the two doses of PPD; 226 students, or 55.93 per cent, changed in their skin reaction from negative to positive; 140, or 34.65 per cent, changed in reaction with the first strength and 86,

TABLE 7

Groups retested after 12 to 18 months' period

NUMBER RE-TESTED	RACE	MATERIALS USED		POSITIVE ON RETESTING		ACTIVE TUBERCULOSIS
		Original test	Second test	*number*	*per cent*	
1,018	White	OT, 0.1 mgm.	OT, 0.1 mgm.	49	4.81	2
404	70% Negroes	OT, 0.1 mgm.	PPD, 2 doses	1st dose 140 2nd dose 86 Total 226	1st dose 34.65 2nd dose 21.28 Total 55.93	4

or 21.28 per cent, with the second strength PPD. Four of these students showed definite pulmonary tuberculosis. In each of these cases the change was noted to the first dose of PPD. The findings in this retested group will be found in table 7.

We realize the difficulty in comparing nonidentical methods in a retesting program but feel it is important to explain the large percentage (55.93) of change in reactions in the second group.

Stiehm, at the University of Wisconsin, found 9.3 per cent additional reactors in an 18 months' period; Lloyd and MacPherson (13), in London, found a 13.6 per cent change in an 18 to 24 months' period, using 3 strengths of OT, 0.01 mgm., 0.1 mgm. and 1 mgm.

We base the discrepancy on the following factors. A 20 per cent in-

crease is allowed for the second test as this is the usual increase and we found it so in all our work. In an explanation of the change in reaction to the first dose of PPD (34.65 per cent) the following factors are involved: (*a*) There were three open cases attending school in the latter group—this contact may have been a very important factor as suggested by Schuman (14); (*b*) the higher potency of PPD in weaker dilutions as found by Plunkett and Siegal (11); (*c*) the large percentage of Negro students in this group (70 per cent) with a higher incidence rate of infection.

Myers and Wulff (15) point out the importance of a complete yearly survey to avoid overlooking cases of tuberculosis. Tuntler (16) and his group also point out the necessity of periodic skin testing and X-raying of students and teachers. Weber, Murphy and Holcomb (17) in their survey investigated the source of infection in every positive reactor. In so doing they uncovered three times as many cases in the parents as were found in the students. Weintraub (18) followed 1,041 children positive to tuberculin for 6 months to 5 years. In 547 contacts he found 11 cases of adult-type tuberculosis. In 499 noncontacts, no cases of tuberculosis were found.

From our retesting program we were impressed with the necessity for yearly examinations of high school students. We believe it is particularly important in this age group as many of them, of the lower economic level, do not enter college where they may be retested. We further believe that, to be complete, a tuberculosis case-finding program must have facilities for investigation and segregation of the source of infection.

To terminate our work we conducted a follow-up study of 68 cases of active or suspect pulmonary tuberculosis found by us in the first three years of our program.

Of these 68 cases we were unable to locate 6; 12 are under treatment or periodic observation by a physician; 8 are definitely ill at home but are not under the care of a physician; 7 are dead. The remaining 35 have failed to continue under observation.

Of the seven deaths, one case, diagnosed as far advanced pulmonary tuberculosis in January, 1935, died at home in December, 1936. Three cases had been diagnosed incipient tuberculosis in January, 1934; one died in March, 1934; one in May, 1935, and one in March, 1937. Two cases had been diagnosed incipient tuberculosis in November, 1934; one died in June, 1935, and one in October, 1936. One case diagnosed incipient tuberculosis in January, 1936, died in December, 1936.

The results show, then, that within a period of three years 10.29 per cent of the cases of pulmonary tuberculosis found in the Chicago high schools have died. This survey reveals further, that 11.76 per cent are ill and only 17.64 per cent are under observation or treatment. That these percentages are disproportionate is of course evident and suggests an inadequate follow-up service and a lack of appreciation of the seriousness and necessity for active measures in early tuberculosis.

SUMMARY

We have presented:

1. Our plan of case-finding in the Chicago high schools
2. A tabulation of the results obtained in skin testing 26,000 Chicago high school students during four years
3. A comparison of the various materials and tests used
4. A comparative study in two groups that were retested within 12 to 18 months
5. Finally, a follow-up study of all cases of tuberculosis found by us in the first three years of our program, 1933 to 1936

CONCLUSIONS

The main conclusions derived from this work are as follows:

1. Abandon the Pirquet test.
2. The use of two or more tests is necessary to determine all positive reactors.
3. A periodic reëxamination in the high school student is necessary.
4. Investigation of the sources of infection must be made.
5. Adequate follow-up and care for the diagnosed case are imperative.
6. The seriousness of seemingly harmless lesions, as seen in X-ray films without any clinical manifestations, should be appreciated.

We wish to acknowledge and thank Doctors Morris Snyder and Alberto L. de Guevara for that portion of work that they conducted.

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TUBERCULOSIS CONTROL IN GERMANY[1]

H. R. EDWARDS[2]

It has been the desire and dream of most tuberculosis workers to possess the authority and facilities to supervise the entire populace of a country or a community in a program to control the disease. To-day the German Reich is perhaps in a better position to realize these ends than any other country. They have complete authority and control of the entire populace and it is of the greatest interest to know how effectively they are utilizing their opportunities to apply commonly accepted procedures in the control of tuberculosis.

It is proposed in this discussion to comment particularly on case-finding as a major phase of control because it so readily lends itself to mass action. Germany has some of the best equipped and operated sanatoria and hospitals for the tuberculous to be found anywhere. The administration of her *Fürsorgestellen* has reached a high degree of excellence, as well as other technical and sociological methods. To treat them adequately would require more space than is available in this presentation.

It is not proposed to pass judgment on the political setup of the Reich *per se*, but nevertheless one must be acquainted with its organization to visualize fully the inherent factors that make for mass control.

The organization of the Reich centres at Berlin under *der Führer*. Under his leadership the various governmental activities are delegated to ministers of the various special services.

The Federal Bureau of Health under the Department of Interior and headed by a Minister of the Cabinet is responsible for all health policies throughout the country. The tuberculosis work is under the *Reichs-Tuberkulose-Ausschuss* which is directed by Dr. H. Denker. Each of the five provinces which make up the Reich has a leader appointed by the Central Government. Thus there is the closest control in policies of all activities. This arrangement is flexible, as broad general

[1] These observations were made in Germany in the fall of 1936 on a Fellowship granted by the Oberlander Trust, Philadelphia, Pennsylvania.

[2] Bureau of Tuberculosis, New York City.

policies laid down by the central organization are in turn subject to interpretation and administration in the various provinces. Thus we find in some provinces more active programs than in others, whereas all adhere to certain fundamental procedures. Within a given province we find a varying number of local programs developed on the same principle.

There are political organizations in the Reich which are under the direct control of the Central Government. For the most part they include those age groups in which we find the highest incidence of tuberculosis mortality and morbidity, and in each organization the Government exerts some effort to protect and control the health of the members.

The *Hitler Jugend* or Youth Organization enrolls boys from the age of six to seventeen years. From the age of ten years approximately eighty-five per cent of all boys are enrolled. A similar organization for girls is developing rapidly and at present represents about seventy per cent between the ages of ten and seventeen years. A physical examination is a requirement for all these youths. The X-ray is used only in those with some suspected pulmonary disease.

At eighteen years each male is required to give one year's service to the State. In this group a physical examination is included. After this service the boy is enrolled in the military service for two years where, of course, periodic examinations are made. If he continues in the Army he is subjected to further periodic examinations.

During the past year there has been a movement under way which has now become a regulation that all young women devote a year of work to the State, the same as boys.

Additional thousands of men and women are enrolled in the various military, naval and political organizations of the Reich, and each must undergo regular examinations. Thus it is obvious that, if an intensive drive were made to examine all of these groups as a tuberculosis case-finding project, one would expect not only to find cases among the enlisted groups but as well obtain leads to possible cases of infection in their homes.

The apparent philosophy underlying the present regime in Germany is that the State is paramount; furthermore, that the strength of the State is in a direct ratio to the health of the individual. For years, even before the present regime, great emphasis has been placed on the health and physical well-being of the populace, and certainly there has been no relaxation during recent years.

In view of these facts, is it not then to be expected that we should find in Germany to-day a tuberculosis program incorporating the best methods of case-finding existing in any country?

The fundamentals upon which their program is based are similar to ours, namely, reporting of the tuberculous, supervision of known cases in hospitals or sanatoria, and the examination of known contacts. These principles are at the foundation of any tuberculosis program. Experience indicates, however, that if we confine our efforts to this group alone we are sure to miss many cases that are in asymptomatic stages and who will later come to our attention in an advanced stage. During this period of vague symptoms, unnoticed by the patient, many are infectious and thus unknowingly are spreading disease to countless others before their symptoms become sufficiently clear to send them to a physician.

In Germany the government has under control the greater majority of its youth and young adults who are in the period of life when tuberculosis makes its greatest inroads. The routine physical examinations made of these groups will detect only the obvious lesions. The X-ray has been proved to be the only method which will indicate the earlier lesions. The cost of X-ray films is relatively higher there than here and a routine X-ray of these vast legions would mean heavy expenditures. However, in view of the emphasis on the physical fitness of each citizen such an investment would appear to be sound and logical.

The physicians in Germany, largely because of the cost of X-ray films, have been forced to rely more and more on the fluoroscope, and as a result they have become more proficient with this device than we have in America. It is logical to expect that if it were used in routine examination among all enlisted youth and adults a more effective job could be done than the plan used at present of X-raying only those with suspicious symptoms, following a physical examination.

If a 100 per cent X-ray examination of organized youths and adults were made periodically, even by the fluoroscopic method, and the possible contacts and sources of infection traced into the homes from which they came, it is reasonable to believe that within two decades Germany could practically wipe tuberculosis out of its midst.

In a country where centralized authority has been so highly developed it was somewhat of a surprise to find that in only one province, that of Thuringia, does there exist the legal power to detain forcibly the recalcitrant case. This power would seem to be fundamental in any

program, and should be a matter of form in Germany in view of other accepted regimentation. There have been interesting developments in Thuringia where forcible hospitalization is a matter of law. At the outset there was resentment against the plan, but as time has passed the tuberculous have shown a greater willingness to follow advice, and therefore the demands on the institution at Gera have become less.

THE PROBLEM OF TUBERCULOSIS

The problem of tuberculosis in Germany may best be visualized by studying the mortality rates over a period of years. Prior to the World War, Germany boasted of one of the lowest rates of the great nations. Following that depressing period, in which the people were reduced almost to the point of starvation, there was a sharp rise in 1918 to 230 per 100,000. In 1920 there was a sharp drop to 154 and by 1926 the rate was 98. In 1933 it declined to 73 and estimates for 1935 indicated a continued decline. Thus the rate, while still higher than that in America, has nevertheless shown a remarkable decline. However, a rate of 70 still indicates that there is a great amount of disease, and much of which is not known.

From the standpoint of age groupings Germany shows the same characteristics found in any community, namely, a high incidence during the first year, a decline and low rate until the fifteenth year at which time the rate rises sharply reaching a peak between 60 and 70 years.

Deaths among males since 1922 from birth to the first year have been consistently higher than among females. Between the first and fifteenth year they have not varied widely between the sexes. Between 15 and 30, since 1924 the female rate has exceeded the male, whereas, between 30 and 80 in all years the male rate has been higher than that among females.

As the population is almost completely German-born there are no particular problems of racial differences as noted in America. The reports of the *Reichs-Tuberkulose-Ausschuss*, 1935–1936, indicate 1,291 *Fürsorgestellen*, or dispensaries, operating in the Reich, with 8 more for the Free State of Danzig. Two hundred sixty-five of them are operated on a full-time basis, the remainder on a part-time basis as periodic clinics in rural areas.

These *Fürsorgestellen* serve a population of 61,431,115 or 92.9 per cent of the German State and 100 per cent of the Free State of Danzig. During the period of the report there were recorded 958,358 individuals

carried forward from the previous year, with 468,904 new individuals examined during the period. The number of new examinations represented 75.6 per 10,000 of the entire population of Germany and 94.8 per 10,000 of Danzig. It is interesting to note that 115,881 of these individuals were referred by physicians.

In Stettin is located perhaps the best organized program in the Reich. It was reported by Dr. Brauning that over 100,000 of the 370,000 population had been examined in his dispensary, which is a ratio of 2,702.7 per 10,000 and indeed a commendable achievement; yet the death rate per 100,000 in Prussia, the province in which Stettin is located, is not lower than for the Reich as a whole.

The relationship of the clinic and physician in Germany is quite different from that in this country. The *Fürsorgestellen* attempt no treatment and exist primarily so that the State may know the status of the case. The report of the physician may be acceptable in this regard but for the most part all such information is obtained by examination in the clinic.

Thus it becomes immediately apparent that the problem of tuberculosis in the German Reich is in most respects similar to that in this country, also that the effort to control the spread of disease should be directed to the adolescent and young adult groups. The Reich has one advantage that we do not possess, namely, the universal control of all persons within those ages. The fluoroscope in competent hands, and it may be said that such is the case in Germany, can be a more valuable and effective means of discovering early and established lesions than by the routine physical examination. It is relatively inexpensive to purchase, the upkeep is almost negligible and thus the unit cost per case is very low. If this method were used routinely on all persons enrolled in the various organizations it would certainly bring to light many cases unrecognized in an early curable stage of the disease. The repetition of this procedure during the period in which the person is in service would then render a complete service.

It is believed the X-ray film would be far superior as it provides a tangible means by which more than one observer can study the case and eliminates the possibility of individual error. As a permanent record of the individual it would be unsurpassed and would add valuable information to the existing file of records on each person. Germany has developed a very high grade of paper film at a cost far below celluloid. If a rapid X-ray camera similar to the Powers equipment used in this

country could be utilized the job of mass surveys would be greatly simplified and produced at the minimum of cost.

In New York City since 1933 the Department of Health has routinely X-rayed approximately 80,000 persons on Home Relief, 15 years or older. In all instances the persons X-rayed have attended voluntarily and, depending on the area served, the response has been from 25 to 50 per cent of those approached. It is fair to assume that among those refusing to be X-rayed there were many who had symptoms or reasons to believe they might be tuberculous who refused to attend clinic, because of the prevalent fear of the disease. Of the total who did attend and were apparently without symptoms we have consistently found on an average of three per cent with manifest parenchymal lesions of the adult type, the percentage of disease varying with certain racial groups, reaching 6 per cent among those of Porto Rican extraction. Furthermore, our experience shows that about three-fourths of the disease found is in the early minimal stages when its cure is more prompt and at a great economic saving to the community. This experience has been corroborated by other workers using a similar method, and we are, therefore, convinced that the ultimate control of tuberculosis depends upon the development of a mass survey of apparently well persons within those age groups showing the peak of tuberculosis mortality and morbidity. These surveys should supplement the regular diagnostic clinic service for known cases and their contacts.

The utilization of this principle by a country like Germany where the State has supreme authority and control of its population should within a reasonable period detect and control all of its tuberculous. Considering the many technical advances made in the Reich it is believed that they are failing to utilize one of the most effective weapons in the control of a preventable disease that is responsible for a wastage of over 47,000 lives each year.

BOOKS

Tuberculosis and Leprosy. The Mycobacterial Diseases. Edited by Forest Ray Moulton. Pp. 133, with 43 illustrations, Symposium Series, Vol. 1, The American Association for the Advancement of Science, 1938, cloth, $2.50.

By MAX PINNER

The papers collected in this book were read at a symposium arranged by The American Association for the Advancement of Science. According to the aim of this Association, these papers are semipopular, designed to be understood by the educated layman without special technical knowledge. The program committee deserves high praise not only for bringing together these authors who are all excellent representatives of the research work on the more basic phases of tuberculosis, but for assembling the speakers in such a way that the breadth of scientific work and the totality of the problem are shown in a well planned and impressive manner.

This symposium summarizes most of the significant advances made during the last ten or twenty years and it indicates the main avenues of approach that are actively used at the present time. It is particularly hopeful that the unsolved problems are attacked from a multiplicity of angles, representing not only a concerted attack, but promising well for an eventual synthesis of a great variety of different facts.

The nature of the group of microörganisms, called *mycobacterium*, is discussed in their biological aspects by Kahn, in regard to their chemical composition by Anderson, Heidelberger, Menzel and Seibert whose important contributions to these fields are well known to the readers of the Review. Two particularly significant developments are presented by Lurie and by Sabin; the one is able to show how the genetic character of the host is a variable of great importance in determining the pathological features of the disease, while the other, based on the work by Smithburn, emphasizes the genetic character of the bacillus. By controlling both these variables, which has become possible through Lurie's and Smithburn's work, the complexities of tuberculosis are brought considerably closer to understanding. The host-bacillus relations are discussed by Corper, indicating clearly that they must be encompassed in a wider field than the one confined to the traditional ideas of immunity and allergy.

A large section is devoted to tuberculosis and allied diseases in animals. Again, each subject is discussed by an author well known for his own contribution to the field that he discusses.

The last section is concerned with leprosy. The paper by Soule and McKinley on the bacteriology of leprosy—which includes a fascinating sketch of the historical development—appears to be particularly noteworthy for the broad and lucid information that it conveys. The present knowledge of leprosy is well rounded out by the other papers in this section.

Long's final summarizing paper points out clearly the bacterial and host features that the diseases caused by *mycobacterium* have in common, and it epitomizes what appear to be at present well founded facts, clearly formulated problems and likely directions for further research.

This monograph should be useful for anyone who wishes to obtain, in readable and simple form, authoritative information on the present status of our knowledge of mycobacterial diseases.

FERDINAND SAUERBRUCH AND LAURENCE O'SHAUGHNESSY: *Thoracic Surgery. Pp. 394 + viii, with 215 figures and 15 plates, Baltimore, William Wood & Company, 1937, fabrikoid, $13.50.*

By E. F. BUTLER

This book will be gladly received by the English speaking profession to whom the original works of Sauerbruch are not easily accessible. The format is pleasing and the English is good. The extensive bibliography gives an impartial list of the important world literature up to 1937. The illustrations, which are generous in number, deserve special commendation and praise.

Sauerbruch's position in thoracic surgery is equalled by few. For more than a third of a century he has been actively identified with the development of this relatively new field. His clinical work has been based on carefully controlled experimental investigations. Sound physiological reasoning underlies all discussion of surgical measures. If the general tone appears dogmatic, it must be forgiven in view of the foregoing facts.

The work is admittedly a "revised and abridged" translation. The translator, O'Shaughnessy, is known to be a devoted follower of the author, and it is apparent that the original spirit and meaning have been carried over into the English edition. In the process of abridgment, however, the original German edition of 2,448 pages has been condensed to 394 pages. This may explain in part the dogmatic tone and the lack of critical evaluation of the work of others.

From time to time a decidedly British flavor crops up. It is specially apparent in the section devoted to reëstablishing cardiac blood supply. There is no reference to any American work on this subject.

The space allotted to the surgery of pulmonary tuberculosis amounts to

only 43 pages. The discussion is necessarily brief and can be taken as no more than a statement of the author's present opinion regarding the indications for and value of the several procedures included under *Collapse Therapy*. Likewise the descriptions of surgical technique represent the preferences of one individual clinic. For the American phthisiologist without surgical training, this work is not as valuable, nor is it as safe a guide, as the books by Alexander or Graham.

Because of the general excellence of the book and the value of the opinions expressed therein, this work (or the German original) should be in the hands of all who are seriously interested in thoracic surgery.

SIR ROBERT W. PHILIP: *Collected Papers on Tuberculosis. Pp. x + 460, Oxford University Press, London, 1937, cloth, $7.50.*

By JABEZ H. ELLIOTT

Sir Robert Philip graduated in medicine at Edinburgh in 1882, the year in which Koch demonstrated the tubercle bacillus as the specific cause of tuberculosis. He spent the next year in study on the continent where the importance of the discovery made a marked and lasting impression on his future life and work. While clinical and laboratory workers everywhere were investigating methods of treatment, Sir Robert while not neglecting this aspect of the disease devoted earnest thought to methods of prevention and control, and may fairly be said to be the pioneer in the systematic organization of an antituberculosis campaign. In 1886 he proposed the erection of a special tuberculosis department at Edinburgh which saw fruition in 1887 in the inauguration of the first tuberculosis dispensary, The Victoria Tuberculosis Dispensary. Here was initiated the dispensary control of tuberculosis, through case-finding, examination of contacts, visiting nurses, domiciliary and sanatorium treatment, gradually extending to include hospital and sanatorium treatment for advanced and early cases, notification, open air schools, farm colony, auxiliary social service organizations and the many services requisite for a complete antituberculosis campaign including prevention, study and treatment. The National Tuberculosis Association at its 1937 annual meeting marked the fiftieth anniversary of the founding of the world's first tuberculosis dispensary by devoting a morning session to a symposium *The Evolution of the Tuberculosis Dispensary*, in which fitting tribute was paid to Sir Robert Philip and his pioneer work.

The volume of *collected papers* presents some twenty-four of Sir Robert's addresses and papers dealing with various aspects of tuberculosis published during the half century of his active and productive professional life. These

illustrate in chronological sequence the lines of his constructive thought over this long period. It is a companion volume to *The Control and Eradication of Tuberculosis* published as a tribute to Sir Robert in 1911 by a large group of his students and friends in Europe, America and the British Isles, under the editorship of Halliday G. Sutherland.

It is a work which should be in the library of every hospital and dispensary, of every physician and director working in the control of tuberculosis. It is stimulating and invigorating. The breadth of vision revealed in the addresses, the steady relentless drive toward prevention while providing for treatment, makes the volume a desirable one to place in the hands of the younger worker in the field of tuberculosis.

We rejoice in knowing that Sir Robert's health, which prevented his attendance at the Milwaukee meeting last year, has sufficiently improved to allow him to see the book through the press. May he long be spared to see the steadily increasing results of his work in coördination of effort.

ÉMILE SERGENT: *Quelques vérités premières (ou soi-disant telles) en pneumologie clinique. Pp. 81, Masson et Cie, Paris, 1937, paper, 24 fr.*

By MAX PINNER

It is peculiarly difficult to give a valid account of this book. It is not a textbook for the beginner, although it contains many of the simplest and most basic facts that he should learn early; it is not a postgraduate treatise, although the man well versed in chest diseases will probably benefit most by it, and surely will enjoy it most; it is not a scientific methodical discussion because its tenor is wisdom rather than science, its form is aphoristic rather than continuous. It should be read not for factual information, but for a polish of such information already on hand. To define its contents and its aims is delusive; it does not fit into any established pigeonhole.

This book leaves the reader with the feeling that he has been on clinical rounds with a man of profound experience, of broad clinical and scientific knowledge, of unusual amenities. One has listened to brief but well selected remarks on how to approach a patient as a diagnostic problem. You are supposed to know the techniques, but your guide tells you the pitfalls to avoid, he teaches you to discriminate between the essentials and the frills. You may not have learned new facts, but you are likely to have learned new directions in attitude, emphasis, concepts. And this is exactly the aim of this treatise, as stated in the introduction: ". . . to suppose that I am with him (the reader) in the specialized wards of my clinical service. . . ."

Professor Sergent, in this book, does not support his statements by proofs, this is not in the nature of the book; he makes pronouncements.

I received once from the Editor of the REVIEW the commentary to a paper: "It takes a pope to make pontifical statements." Here is the pope, and here are his statements.

R. C. WINGFIELD: *Pulmonary Tuberculosis in Practice. A Modern Conception. Pp. viii + 122, with 20 figures and 21 charts, Baltimore, William Wood & Company, 1937, fabrikoid, $2.50.*

By HENRY STUART WILLIS

This little book is written to point out certain orienting facts about tuberculosis to the general practitioner who is appealed to for coöperation with the Public Health Service and who is told that his job is to diagnose but not to treat tuberculosis. It is an admirable attempt to correlate pathological and clinical data in this disease. The disease is portrayed in a somewhat elaborate yet understandable classification which represents "the possible spontaneous developments of the initial lesion of chronic pulmonary tuberculosis." To one who deals with tuberculosis the classifications seem defined too sharply and too much as entities and the conception appears to be that tuberculosis tends to be a static, predictable disease. The book stresses well the transiency of symptoms, paucity of signs and need of the X-ray for diagnosis, particularly in the early case. It indicates clinical alertness on the part of the author, and it offers good advice as to follow-up care of the patient after discharge from the sanatorium. It carries a lucid, brief story of haemoptysis in which, however, use of morphine is still advocated, pleurisy with effusion, spontaneous pneumothorax, ischiorectal abscess, tuberculin reaction, tuberculous laryngitis.

One cannot but wonder why sanatorium treatment for patients of older years is said to be contraindicated. Do not the relatives and the public rate consideration and protection? Are not the coughing and but slightly ailing grandfathers and grandmothers now known often to be potent spreaders of tubercle bacilli? Exception may be taken to a hard and fast grouping of "closed" and "open" cases, and especially with the conception that the former is without symptoms but that the latter has them. Recent careful laboratory studies in this country have revealed tubercle bacilli in the sputum in 35 per cent of so called closed cases of tuberculosis of the lungs; and protracted, repeated examination showed them to be present in 100 per cent at some time during the course of the disease. Many in this country will not agree with the contention that secondary streptococcal infection of the tuberculous lesion is generally responsible for symptoms and for liquefaction. These will cite

the "toxicity" associated with many of the more acute manifestations of tuberculosis and will think of softening and liquefaction of "sterile" tuberculous abscess of bone, joint or kidney as indicating inherent capacity of pure tuberculous lesions to liquefy.

The book should impress the general practitioner with the potentialities and gravity of the tuberculosis problem and with the importance of early diagnosis and treatment. All will agree that the author envisions a fruitful future for diagnosis when he says "it is to be hoped the day will come when the X-ray will be as freely used as the clinical thermometer."

L. S. T. BURRELL: *Recent Advances in Pulmonary Tuberculosis, 3rd edition. Pp. viii + 220, with 48 plates and 22 text figures, P. Blakiston's & Co., Inc., Philadelphia, 1937, cloth, $5.00.*

By RICHMOND DOUGLASS

This handbook is intended for general practitioners and students as a guide to the modern methods of diagnosing and treating pulmonary tuberculosis. The author takes a broad view of the term "Recent Advances" and presents the standard procedures in their modern form, recognizing that changes have been made in the past ten years. The volume is, therefore, comprehensive and not limited to a review of new work. It is concisely written and conclusions are well expressed. A brief bibliography is appended to each chapter.

The table of contents includes chapters on *Immunity and Infection, Prevention, Diagnosis, Radiology, Complications, Tuberculosis in Children and Bovine Tuberculosis, Classification and Types of Disease,* and six chapters on treatment under the headings *General, Medicinal, Sanatorium, Climate and Light, Artificial Pneumothorax,* and *Oleothorax and Surgery.*

The material presented is colored by the nationality of the author (British). The vital statistics quoted are those of England and Wales, climate is discussed with reference to Continental resorts, and the attitude toward sanocrysin and gold salts, though moderate, is more favorable than that of American phthisiologists. The use of BCG is accepted with reservations and the suggestion that its use would be most fruitful just before and during puberty. Exercise in its more strenuous forms is advocated, references being made to gardening and trenching, and a walk of four miles in an hour is suggested as a test.

The point of view in general is, however, balanced and radical procedures are discouraged. It is recognized that dangers, though rare, do exist in pneumothorax, "so that pneumothorax should not be undertaken as a routine in every early case." Thoracoplasty is discussed briefly, including Semb's modification, and the point is made that although it has saved lives this is not

a good operation, like lobectomy, where the disease is actually removed. "The function of the physician is to prevent the patient from reaching that stage in which such serious surgical procedures become necessary."

The methods advocated are not on the other hand unduly conservative. The recommendation is made, for instance, that, when a collapsed lung becomes bound down by thickened pleura and reëxpansion is impossible, the pneumothorax cavity is to be regarded as a source of danger, whether an effusion be present or not, and it should be closed by thoracoplasty. Citation may also be made of the chapter on *Radiology* which includes mention of the tomograph and reference to its field of usefulness.

Those who may be familiar with the first edition of this book, published in 1929, will find that extensive rewriting and additional text have added 100 pages to the present volume. The placing of the excellent X-ray reproductions at the end of the volume, with appropriate references to the text, is a satisfactory solution of the problem presented by the use of two types of paper in the book.

S. A. REINBERG: *Pulmonary Tuberculosis and Manifestations of Involvement of the Bronchial Passages. (Russian) Pp. vi + 198, with atlas of roentgenographic reproductions pp. 110, including 184 illustrations, Leningrad Tuberculosis Institute, Biomedgiz, 1937, Leningrad Branch.*

By WILLIAM A. ZAVOD

The book comprises a collection of nine dissertations, on the involvement of the bronchial passages in pulmonary tuberculosis, by several members of the Leningrad Research Institute in Tuberculosis and the Department of Roentgenology of the Kirov Postgraduate Institute. The subject matter is interesting and the work important since comparatively little has been written on the fate of the bronchial passages in pulmonary affections. Indeed, many changes that occur in the pulmonary parenchyma as sequelae to pulmonary disease are actually end results of concomitant involvement of the bronchial passages. Atelectasis, emphysema, fibrosis and bronchiectasis are frequently associated with pulmonary tuberculosis and the direct cause of these is most often the involvement of the bronchi.

The work reported upon in this book attempts to throw some light on the subject. The first two papers deal with experimental investigation. M. S. Perlin injected 117 human lungs within twenty-four hours after death with a contrast paste under fluoroscopic control. In his collection were 34 normal lungs, the remainder consisted of pneumococcic pneumonias, lung abscesses, bronchiectasis, pulmonary oedema, emphysema and all forms of pulmonary

tuberculosis. The injected specimens were roentgenographed from different angles and a total of 423 exposures studied. Summarizing his findings the author concludes as follows: (*1*) No changes in the bronchial passages were found in pneumococcic pneumonia, pulmonary oedema, noncaseating tuberculous bronchopneumonia, productive miliary tuberculosis and acinous and acinous nodose productive tuberculosis. (*2*) Obstructive changes in the bronchial passages were found in pulmonary atelectasis, pulmonary emphysema, cirrhotic pulmonary tuberculosis, caseating tuberculosis and lung abscess. (*3*) Bronchiectasis was found in 25 per cent of all cases of pulmonary tuberculosis studied. (*4*) Emphysema was found in over 50 per cent of all tuberculous lungs. The author emphasizes perfect filling of the bronchial tree in all cases of pneumococcic pneumonia, contrary to the observations by Coryllos and Birnbaum.

A. D. Weisberg in the second paper reports on experimental atelectasis and obstructive emphysema induced in 33 dogs. The author's conclusions are: (*1*) Extensive pneumonic changes around the atelectatic areas are found in all cases of experimental atelectasis. (*2*) Roentgenological study showed that atelectasis or emphysema (depending whether the obstruction was complete or valvular) occurs within 1, 5 to 6 hours following the obstruction and the changes disappear 24 to 48 hours following the removal of the obstruction.

The other seven articles are clinico-roentgenological studies of the bronchial passages in tuberculous bronchoadenitis, various forms of pulmonary tuberculosis, the tuberculous cavity in relation to involvement of the bronchial passages, atelectasis following haemoptysis, atelectasis in artificial pneumothorax, atelectasis in pleural effusions, and massive atelectasis following thoracoplasty. A few of the more important conclusions made by the authors of these papers are: (*1*) Atelectasis due to pressure of tracheobronchial tuberculous lymph nodes is usually lobar and most often involves the right lower lobe. (*2*) Perihilar inflammation often seen in tuberculous adenitis is in many cases due to an atelectatic process. (*3*) Artificial pneumothorax will often relieve the obstruction caused by an enlarged tuberculous node. (*4*) A high negative tension is not always present in atelectasis. (A. M. Rabinovich.)

(*1*) Obstructive atelectasis and obstructive emphysema nearly constantly accompany acute forms of tuberculosis. (*2*) Neglected chronic atelectasis always leads to multiple bronchiectasis. (N. F. Pershina.)

(*1*) The dynamico-functional manifestations of tuberculous cavities can be understood in the light of the new teachings of involvement of the bronchial passages, especially the bronchi draining the cavity. Cavities can be divided into those with open drainage, limited drainage due to valvular mechanism, and obstructed drainage. (*2*) Cavities with open drainage can change their volume with forced respiration and during cough. Cavities with a valvular

mechanism type of drainage can increase in volume two to three times, especially in the presence of pneumothorax. Cavities with obstruction to drainage disappear due to absorption of the air in the cavity by the blood circulating in the cavity walls with subsequent scarification due to fibrosis of the collapsed cavity. Collapsed cavities can open again when drainage is reëstablished. (I. N. Ivanov.)

Infiltrations appearing in a lung following haemoptysis are in many cases atelectatic processes due to obstruction of the pulmonary bronchioles by blood clots. They disappear within a short time, often the same day. (A. M. Rabinovich.)

(*1*) Pneumothorax is frequently the cause of atelectasis due to mechanical change in the bronchial passages. (*2*) Dense homogeneous shadows appearing following the induction of pneumothorax are expressions of atelectasis. (*3*) The illusion of the so called "selective collapse" is nothing more than a collection of air over an atelectatic tuberculous area. (N. F. Pershina.)

(*1*) Massive pleural effusions can cause pulmonary atelectasis because of kinks that may appear in the bronchial stems following the compression of the lung by the fluid. (*2*) The heart and mediastinum in these cases are displaced toward the involved side because of the atelectasis not because of the pleural adhesions. (*3*) Atelectasis in the presence of a pleural effusion in a previously noninvolved lung is a serious complication. The fluid should be removed to facilitate reëxpansion of the atelectatic lung. (*4*) Atelectasis can be complicated by pleural effusion. The effusion in those cases has an atypical roentgenographic appearance and the localization corresponds to the seat of the atelectasis. (N. F. Pershina.)

(*1*) Nearly every case of thoracoplasty is complicated by atelectasis and thus is the postoperative rise in temperature explained. (*2*) Interference with the respiratory function of the lung due to pain in the operated hemithorax is responsible for the atelectasis following thoracoplasty. (A. I. Mariupolsky.)

Probably the most important contribution of the book is to be found in the first paper by Perlin, since, I believe, it is the first report of the state of the bronchial passages in various pulmonary diseases, carried out on a large scale under roentgenoscopic and roentgenographic control. That the dynamics of the bronchial tree and the thorax as a whole, antemortem, are important factors influencing the patency of the bronchial passages is beyond doubt. The work is, therefore, offered with that limitation in mind. The importance of atelectasis in pulmonary tuberculosis has been emphasized before in this country and abroad (Coryllos, Stivelman, Rössle, Fleischner and others). Pershina, however, introduces a novel approach in attempting to explain shrinkage and pulmonary fibrosis following some tuberculous effusions in patients with or without artificial pneumothorax, on the basis of bronchial stenosis and atelec-

tasis. While it is hypothetically possible that in cases of pleurisy with effusion some bronchi in the involved hemithorax may become kinked and occluded causing atelectasis, it is not the case, in the reviewer's opinion, when a tuberculous effusion occurs in a patient with pneumothorax. The shrinkage and fibrosis of the involved hemithorax, in some of those cases, are pleural in origin, since at postmortem the pulmonary, costal and diaphragmatic pleurae are often over one centimetre thick and undergoing obliterative changes without evidence of any greater collapse in the lung than that seen prior to the occurrence of the pleural effusion. Mariupolsky's conclusion that atelectasis following thoracoplasty is due to interference with the respiratory function because of postoperative pain, is somewhat naive. Surely, the removal of the osseous support from the chest-wall is a more potent factor in producing atelectasis immediately following the surgical interference.

S. A. Reinberg, summarizing the articles, at the end of the book, points out the necessity of further investigation of the pathomorphological changes of the bronchial passages in pulmonary tuberculosis. He suggests that further study may open up new avenues of therapeusis.

The articles are well written and ample bibliographies are appended. The roentgenographic reproductions are poor, but quite an improvement over the reproductions of several years ago.

Tuberkulose (A Postgraduate Course of the Academy for Medical Postgraduate Education, Berlin). Edited by H. Ulrici and O. Koch. Pp. 147, with 42 illustrations, Berlin, Verlag von Julius Springer, 1937, paper, RM 6.60.

By MAX PINNER

If the existing knowledge of diagnosis and therapy of tuberculosis could become the common possession of all practicing physicians the battle against the disease would probably be more than half won. Therefore, books that help to accomplish such aim are of signal importance. Such books should contain all the essential information; they should be brief, concise, readable, simple without sacrifice of accuracy. According to such standards, this little collection of postgraduate lectures comes as close as any book known to this reviewer to the desired aim. It is particularly noteworthy that in spite of brevity and simplicity it is scientifically accurate and reasonably complete, even in regard to the fundamental topics of pathology and respiratory physiology. In addition, the illustrations are of such high quality that they exceed those of many expensive textbooks.

The methods of presentation in this book might well serve as guides in the preparation of postgraduate lectures and didactic papers.

A Five-Year Study of Tuberculosis among Negroes, Report of the Committee on Tuberculosis among Negroes. Pp. 77, National Tuberculosis Association, New York, 1937, paper.

By VIOLET H. HODGSON

The five-year study by the Committee on *Tuberculosis among Negroes* is an "attempt: (*1*) To stimulate interest in the problem of tuberculosis among Negroes on the part of state and local tuberculosis associations, health departments, the medical profession, and the general public. (*2*) To investigate current administrative practices in the control of tuberculosis among Negroes in all states and cities with large colored populations and make every effort to secure wider utilization of such procedures as in its judgment seemed most effective. (*3*) To devise new techniques which would be helpful."

The extent of the problem is portrayed in tables and charts showing the ratio of the colored to the white mortality for each year from 1910 through 1934. From an extensive analysis of the medical literature, the inference is drawn that the high tuberculosis death rate among Negroes may be attributable to a probable racial handicap complicated by an environmental disadvantage, largely economic.

In advocating effective case-finding methods and adequate facilities for diagnosis and hospitalization with allocation on the basis of annual deaths and not population unit, the relatively meagre economic resources of the Southern States are analyzed and recognized as a problem in reaching the minimum standard. Temporary expedients for isolation and care of the patient (screened porches, Burr cottages, and homes for custodial care) are described with directions for obtaining detailed information on cost of construction and maintenance from agencies which have had experience in their use.

Emphasis is placed on the rôle of the Negro physician in the success of any control program and the establishment of educational facilities whereby the private practitioner and medical student may acquire a reasonable measure of skill in diagnosis and the application of modern treatment methods. An equally important place is assigned to the Negro public health nurse.

The health educational plans in operation in various parts of the country are described and include the wide range of Negro colleges, student health services, grade schools, trained health-education workers, health clubs and newspapers.

Appended are institute programs, a plan for organizing Negro health clubs, and an extensive bibliography.

E. BRIEGER: *After Care and Rehabilitation. Principles and Practice. English text presented to the Conference of the International Union against Tuberculosis, Lisbon, September, 1937. Published by The British Journal of Tuberculosis as a special supplement, No. 4, Vol. xxxi, October, 1937.*

By WILLIAM SIEGAL

Most workers in the United States who are interested in the problem of tuberculosis control still devote most of their time and energy to case-finding, segregation and treatment. On these subjects a vast literature has developed containing many factual data upon which are based the present approaches to, and treatment of, these problems.

As yet, no comparable knowledge is at hand to guide us in the proper handling of still another phase of the tuberculosis program, which, by its very nature, is just as vitally important if such a program is to be complete. That problem deals with the disposition of the tuberculous patient after he is discharged from the hospital, not only from a physical viewpoint, but also from a social economic viewpoint.

This monograph, which is a preliminary study attempting to establish the principles underlying the problem of after-care and rehabilitation, endeavors to estimate the size and the scope of the problems and the ways to deal with them. Of the three divisions of the book, the first, *Prognosis and After-Care*, is particularly valuable since it presents a résumé of statistical analyses and conclusions relating to the after-care of patients discharged from tuberculosis hospitals, both before and since the present era of modern therapeutic aids in the treatment of this disease. There is evidence that, in Europe at least, there is an increasing percentage of sputum-positive cases which become sputum-negative (+ −), that the survival rate of even the sputum-positive cases (+ +) is increasing and that the case fatality rate is decreasing. In spite of the great stride made by therapy, in fact, as a result of active therapy, as the numbers of semihealed cases increase parallel with the numbers of healed, the problem of temporary and permanent after-care becomes more urgent.

Because of these factors, after-care becomes an indispensable complement of a system of therapy, and temporary after-care as regards organization must be closely connected with sanatoria and tuberculosis hospitals.

In the second division of the book, on *Social Rehabilitation*, the author states:

"We have now-a-days to reckon with the fact that the open tuberculous who are capable of earning are either employed in professions unsuitable both for themselves and for their fellow workers or unemployed and therefore living in conditions which are unsuitable for themselves, their families and their environ-

ment; and there seems no method possible for the authorities to incorporate these patients systematically into industrial life, so that the maximum use could be made of their economic value.

"Up to the present time sufficient attention has not been paid to the fact that this group of tuberculous patients is in number and in social hygienic importance at least equal to the group of arrested cases for whom adequate conditions can be procured in normal industrial life, and also to the group of progressive + + cases for whom social hygienic measures must be made."

That, and the fact that success or failure of social rehabilitation must not be decided by industrial economics alone, seem to state the case clearly and succinctly. The factors involved in estimating the working and earning capacity, the economic value, and the social readjustment of the discharged tuberculous wage earner are discussed at some length, with a special chapter on the costs to the community in undertaking such a program of physical and economic rehabilitation as compared to sanatoria treatment and "laissez-faire."

In the third section are presented the different approaches which have been made to the problem of institutional care and after-care in this country and abroad, with comments on each experimental and established program ending with the Papworth Scheme and the Preston Hall Sanatorium Colony in England. One cannot help but get the impression that to the author these latter two schemes are thus far the most successful.

The author closes with a summary of the conclusions drawn as a result of his investigation, but these convey no idea of the large amount of useful and informative material condensed in the 131 pages of the text. Not for much longer can this problem be ignored. If a scientific foundation for a program of after-care and rehabilitation is to be laid, a careful study of this book is especially worth while, if for no other reason than to reveal the many inherent complexities and potential pitfalls and the large amount of spade work still remaining to be done.

C. V. R. BLEEKER, FREDERICK G. ELTON, EDYTH AHRENS, HARRY A. PATTISON: *Vocational Rehabilitation of the Tuberculous. Pp. 21, Tuberculosis Sanatorium Conference of Metropolitan New York, 1937, paper.*

By EDWARD B. BOSWORTH

The four authors each present one particular approach to the problem of vocational rehabilitation. The various methods of meeting this problem should

prove of interest to those who are attempting to assist the patient leaving the sanatorium in his question of "What next?" Following a discussion of rehabilitation each author presents a local application.

C. V. R. Bleeker discusses the procedure being tried in New Jersey, with the hope of statewide application. A special agent who is a member of the State Rehabilitation staff devotes his full time in one county helping discharged patients to find work and keeping records which will allow evaluation of the results. The worker acts as a liaison between persons certified by the medical staff as being fit to engage in full-time employment and prospective employers.

Frederick G. Elton represents a department of the New York State government which is giving training to selected ex-patients who are physically able to work full time. Following a period of vocational training the individual is assisted in finding work.

Edyth Ahrens discusses how the New York State Employment Agency assists patients in finding work after they have been declared able to work full time following medical studies. The placement of tuberculous individuals is a natural function of the Division of the Handicapped. The author feels that sheltered workshops are needed for a better try-out of applicants before they are referred to a job in industry.

H. A. Pattison discusses sheltered workshops with the aim of hardening the patient before he goes out to compete in industry. During the process of physical rehabilitation of the patient, aptitude tests are given to assist in guiding him in selection of a vocation. During his stay in the institution the patient works at a congenial occupation until his physical condition will permit full-time work in industry.

While it cannot be stated that the problem is being adequately met, the possibilities suggested in these papers are bound to afford stimulation to all interested in rehabilitation.

LOUIS I. DUBLIN AND ALFRED J. LOTKA: *Twenty-Five Years of Health Progress. A Study of the Mortality Experience among the Industrial Policyholders of the Metropolitan Life Insurance Company 1911 to 1935. Pp. 611, with many charts and tables, Metropolitan Life Insurance Company, New York, 1937, fabrikoid.*

By LEONARD GREENBURG

The present volume presents a study of the mortality experience among industrial policyholders of the Metropolitan Life Insurance Company during the twenty-five year period from 1911 to 1935. These mortality records

represent an unusual mass of data covering a very large group of insured persons over a considerable period of time and as such must be regarded as being authentic and as possessing unusual value.

In eleven distinct portions of this volume the mortality from all causes, the trend of longevity and the death rates from various diseases are discussed, as are also the death rates from various external causes.

Of most interest to workers in the field of tuberculosis is a discussion of tuberculosis mortality in five different categories: tuberculosis, all forms; tuberculosis of the respiratory system; tuberculosis of the meninges and the central nervous system; tuberculosis of the intestines and the peritoneum; tuberculosis of the other organs and chronic disseminated tuberculosis.

With reference to all forms of tuberculosis, it is pointed out that this disease has declined steadily in the insured population under review, the standardized death rate having fallen from 224 per hundred thousand to 66.8 per hundred thousand—a drop of somewhat over 70 per cent—the decline in the death rate being 74 per cent for white males and 71 per cent for white females as compared with 55 per cent for colored males and females. The decline in tuberculosis mortality subsequent to the influenza pandemic of 1919 was greater than the rate of decline prior to the influenza pandemic. The report points out that the recent trend in rates of decline "suggests that the forces which combatted this disease have actually reduced the number of infectious foci to a point at which the annual number of new cases is insufficient to maintain the death rate at a constant level under existing conditions." Comparing the United States general population with the industrial experience of the Metropolitan Life Insurance Company, the report brings out the striking fact that rates obtained from these two sources are closely parallel, the Metropolitan rates being somewhat higher due, undoubtedly, to the selected population under consideration.

In discussing the factors responsible for the decline of the death rate from tuberculosis, it is pointed out that the preventive program of the National Tuberculosis Association has spread to every corner of the country and "every village has benefited from the effects of this campaign." Other factors which the report emphasizes are the Framingham, Massachusetts Community Experiment, the rapid extension of clinical facilities in urban areas, the growth of Visiting Nurse Services, medical surveys among school children, the elimination of tuberculous infected cows, the widespread development of sanatoria for hospitalization purposes, the newer methods of therapy, particularly collapse therapy, the protection of industrial workers, the provision of preventive physical examinations and certain other more general demographic factors as well as changes in social and hygienic conditions generally.

In discussing the problem of occupation and respiratory tuberculosis, emphasis is placed on the importance of dust as a causative factor. The high mortality rates from tuberculosis among granite cutters, ax grinders and polishers, gold and silver miners, copper miners and lead and zinc miners are cited as important evidences in confirming this view-point.

The sections of the volume dealing with the subject of accidents is of especial importance and value; it is obvious that a large body of data such as this must contribute greatly to our knowledge of accidental deaths. In this category the discussion of automobile, railroad and streetcar accidents, as well as traumatism by falls is of especial value.

This volume is of fundamental value to the public health worker. There is no doubt that many new studies in the growing field of public health will have their inception as a result of careful study and deliberation of this complete factual presentation of American mortality statistics.

GEORGE SHWARTZMAN: *Phenomenon of Local Tissue Reactivity. Pp. 461, with 67 illustrations and 1 colored plate, Paul B. Hoeber, Inc., New York, 1937, fabrikoid, $7.50.*

By ERNEST WITEBSKY

This book summarizes the experiences collected during the last few years concerning the phenomenon of local tissue reactivity toward certain bacterial agar-washing filtrates. Introduced by a foreword of Jules Bordet it gives a comprehensive and clarifying review of the experimental situation. Thirteen chapters deal with the methods for the elicitation of the Shwartzman phenomenon and with its different aspects. The author clearly demonstrates that the state of sensitization of the local area induced by the first intracutaneous injection cannot be explained by the assumption of a simple nonspecific irritation of the tissue. Shwartzman defends in his book the opinion that this type of local tissue reaction is based upon an entirely different immunological mechanism than the Arthus phenomenon on the one hand and bacterial hypersensitiveness on the other hand. The Arthus phenomenon is a highly specific reaction. The Shwartzman phenomenon is characterized by a definite lack of specificity. Sensitization obtained by the first injection in the case of the Shwartzman phenomenon is induced after the lapse of several hours and remains operative up to four days in sharp contrast to the experimental condi-

tions governing the Arthus phenomenon. There are interesting connections between the tuberculin reaction and the Shwartzman phenomenon. Future experimental work in this direction may lead to a better understanding of the rather complicated factors involved.

The influence of the injection of bacterial agar-washing filtrates upon certain malignant neoplasms of animals is reported in a special chapter. The observation that antigen-antibody reactions may replace the second (intravenous) injection of a potent bacterial agar-washing filtrate reveals a new method for the demonstration of antigen-antibody reactions. The author, however, does not believe that the formation of anaphylatoxins is the cause of this type of reaction. Pathological changes occurring in areas exhibiting haemorrhagic necrotic lesions are described and studied also from the histological standpoint. Reference is made to the possible application of the author's investigations for practical clinical purposes.

The experimental data presented are carefully controlled. A tremendous amount of work has been done in a relatively short time. The reader will learn many important facts brought to light by recent investigations. Shwartzman's book opens new fields for research and practical clinical work which promise to become extremely fruitful. A complete literature as to the subject under investigation is given. The reading of this most stimulating book is a source of valuable information for all those who are interested in the progress of immunology.

J.-M. LEMOINE: *La Thrombose de l'artère bronchique, cause de dilatation bronchique chronique de l'adulte. Pp. 189, with 27 illustrations, Paris, Librairie E. Le Francois, 1936, paper.*

By MAX PINNER

The main thesis of this monograph is that inflammatory obstruction of bronchial arteries is an important, if not the most important, factor in causing bronchial dilatation by interference with the nutrition of the bronchial walls. It is readily understandable that Doctor Lemoine is not entirely satisfied with any of the established explanations for the pathogenesis of bronchial dilatation and that he has, therefore, elaborated Hanot's suggestion as to the rôle played by obstructive lesions in the nutrient vessels of the bronchial structures. A variety of pathological processes that undoubtedly require further study may

cause the occlusive bronchial arteritis; the direct result is dilatation of the involved bronchus and the advent of intrabronchial infection spells the clinical picture of bronchiectasis.

While it seems rather likely that obstructive disease of the bronchial arteries plays a rôle in the pathogenesis of bronchiectasis that hitherto has not received sufficient attention, it is probable that Doctor Lemoine's explanation is an oversimplification and that many other factors are operative. It is probably futile to search for one single cause of bronchiectasis. The mere fact that bronchiectasis is, in more or less conspicuous degree, present in the majority of all cases of suppurative disease of the lungs would indicate the great variety of potential pathogenetic factors.

Doctor Lemoine's study is nevertheless an important study of the pathogenesis of bronchiectasis; in addition to his actual observations on human and experimental material, he presents a clear analysis of the literature, a valuable bibliography and excellent studies of the anatomical and topographical relations of the bronchial arteries. The monograph is competently illustrated. It should well repay careful study for anyone interested in the pathology and pathogenesis of bronchiectasis.

A. HOVELACQUE, OLIVIER MONOD AND HENRI EVRARD: *Treize coupes horizontales du thorax. An atlas, size 56 x 38 cm., drawings by Arnould Moreaux, Librairie Maloine, Paris, 1938, paper, 175 frs.*

By MAX PINNER

This atlas represents thirteen horizontal sections through the thorax of a normal man who had died by trauma. The body was injected with formalin, frozen and the cutting was done with a circular saw. The first section presented is at the level of the third thoracic vertebra and the last section is at the level of the eleventh dorsal vertebra. The plates are in natural size. The lithographic reproductions show every detail visible in the anatomical preparations, and each figure is accompanied by a simple outline in line-drawing of the same size in which every detail is marked by its anatomical name.

These plates afford an excellent guide to the topographical relations within the chest and in the thoracic wall which should in many instances be equally helpful to the internist and to the thoracic surgeon. The reproductions are so strikingly clear in every detail that it seems perfectly natural that they are

not accompanied by any text, save a brief note that explains the technique of the work.

This atlas deserves unqualified praise and wide distribution for the teaching and studying of anatomy, thoracic surgery and internal medicine.

DONALD MAINLAND: *The Treatment of Clinical and Laboratory Data. Pp. 340 + xii, with 23 figures in the text, Oliver & Boyd, Edinburgh, 1938, fabrikoid, 15s.*

By AARON EDWIN MARGULIS

This is an introductory text in statistics written by an anatomist for medical and dental workers. The stated aim is to show why and how allowance should be made for the element of "chance" in all observations and judgments in medicine, so that a clinician may get the most sound benefit from his own observations and from the observations of others. Any clinician aware of this necessity can achieve this aim by studying this book. The reviewer knows of no other statistical text quite so suited for this particular purpose. The author shows keen appreciation of the statistical needs of medical workers and the probable extent of their prior knowledge of statistical concepts and techniques. The presentation is a "popularization" in the best meaning of that much misused term, namely, "logical simplification." Methods and techniques are derived from primitive statistical concepts by steps so graded that any intelligent educated person can follow them with insight and understanding. And always the end to be achieved is kept clearly in view so that the whole has cogency and necessity particularly since the illustrative material is medical data. The subject matter discussed will very likely cover 99 per cent of the statistical needs of medical workers. And with this text as a background, the solution of any residual problems can be sought in the more specialistic treatises such as those of Yule and R. A. Fisher.

PAUL DE KRUIF: *The Fight for Life. Pp. 342, Harcourt, Brace and Company, New York, 1938, cloth, $3.00.*

By MAX PINNER

This is a story of preventable death that is not prevented, of avoidable disease that is not avoided, of obtainable health that is not obtained. It is the call

of the propagandist against ignorance in the public and in the profession; it is his impassioned plea for enlightenment, for good-will and for the financial funds necessary to achieve in practicable application what scientific study has shown to be possible. The story is gruesome, the call is loud and often raucous, the plea knows no consideration but its final aim. But—so it is plainly written between the lines—the voice must be loud because the ears to hear it are deaf.

De Kruif's propagandistic fireworks are unquestionably effective, but is it necessary to distort facts and reality in order to simplify problems? Is it wise to state as definite promises what the enthusiast may see as distant hopes?

But, underneath the gory colors of his tales, behind the wailing voice of the accuser, there remains the nucleus of simple truth, "the frustration of science." Medical science has accumulated an arsenal of weapons against preventable death that remain ineffectual for lack of money. De Kruif shows dramatically (one is constantly tempted to ask: possibly *too* dramatically?) how, just for lack of funds, available knowledge cannot be applied to the totality of the population.

It would hardly be wise to recommend de Kruif's books as a source of factual information, but this book is valuable because it shows up a deep gap in our civilization, because it seeks to arouse a new attitude of collective responsibility toward health.

Hermann M. Biggs said, "health is purchasable;" de Kruif would undoubtedly agree, but he would probably add that the majority of our people haven't the cash to pay for it, that health is purchasable not by the individual for himself, but only by the community for all.

Brief Comment

DONATO VIVOLI AND JOSE PERONCINI: *Anatomia patologica de la tuberculosis del corazon. Reprinted from Revista Argentina de Tuberculosis, Buenos Aires, April–September, 1937. Pp. 69, with 33 illustrations, paper.*

This is a thorough discussion of the pathology of tuberculosis of the heart with an extensive bibliography. The authors have observed and report 60 cases of tuberculous pericarditis, 24 cases of tuberculosis of the myocardium and 4 cases of tuberculous endocarditis; to this are added 34 cases of nontuberculous endocarditis associated with tuberculosis elsewhere in the body. Representative and well reproduced illustrations complement the text.

Third Symposium on Silicosis. Edited by B. E. Kuechle, Employers Mutual Liability Insurance Co., Wausu, Wisconsin, 1937. Pp. 266, paper.
This is an official transcript of the Third Silicosis Symposium held in connection with the Trudeau School of Tuberculosis at Saranac Lake, New York, June 21 to 25, 1937, and contains the following articles: *The Significance of the Silicotic Problem* by L. U. Gardner; *Etiology of Silicosis* by R. R. Sayers; *Dust Concentrations and Their Measurement* by Philip Drinker; *Pathology of the Pneumoconioses* by L. U. Gardner; *Pathology of the Pneumoconioses. Correlation of Pathologic and Roentgenologic Findings* by L. U. Gardner; *Physiology of the Fibrotic Lung* by W. S. McCann; *Roentgenologic Aspects of the Normal and Silicotic Lung* by E. P. Pendergrass; *Roentgenologic Diagnosis of Silicosis* by H. L. Sampson; *The Clinical Picture and Diagnosis of Silicosis with Consideration of Disability* by A. R. Riddell; *Control—Medical Aspects* by A. R. Riddell; *Control—Engineering Aspects* by Philip Drinker; *Administrative Aspects of Silicosis* by D. E. Cummings; and *Legislative Control and Compensation* by T. C. Waters.

R. Douglas Howat: *Elements of Chromotherapy. The Administration of Ultra Violet, Infra Red and Luminous Rays through Colour Filters, with Foreword by Sir Henry Gauvain. Pp. 106 + xvi, with 20 illustrations, The Actinic Press, Ltd., London, 1938, cloth, 8/6d.*
A discussion of light therapy that is as unscientific in its physical foundations as it is fantastic in its therapeutic applications.

Books Received

Jean Downes and Clara R. Price: Tuberculosis Control in the Mulberry District of New York City. Pp. iv + 33, with 14 tables, reprinted from The Milbank Memorial Fund Quarterly, vol. xv, no. 4, October, 1937, paper.

Questions Cliniques d'Actualité, Leçons professées à la charité service du Professeur Sergent. Pp. 317, with 57 figures, Masson et Cie, Paris, 1937, paper, 65 fr.

X. Conférence de L'Union Internationale contre la Tuberculose, September 5–11, 1937, Lisbonne. Pp. 567, paper.

Julio Palacio and Egidio S. Mazzei: La atelectasia pulmonar. Pp. 159, with 76 illustrations, Buenos Aires, 1937, paper.

WALTER SCHWENK: Die Klinik der primären Lungentuberkulose des Kindes. Pp. 53, with 40 illustrations, Ferdinand Enke, Stuttgart, 1938, paper, 5 RM.

ASHWORTH UNDERWOOD: Tuberculosis for Nurses. Pp. xix + 404, with 53 illustrations, Baltimore, William Wood & Company, 1938, fabrikoid, $3.25.

FRANZ DEUTICKE: Die Chirurgie des Kropfes. Pp. viii + 112, with 51 illustrations, Leipzig and Wien, Franz Deuticke, 1938, paper, Mk. 7.

Cuarto Congreso Pan-Americano de la Tuberculosis, Vol. 1, 1937, pp. 333; Vol. 2, 1938, pp. 281, Santiago de Chile, Imprenta Universitaria, paper.

Internships and Residences in New York City, 1934–1937. Their Place in Medical Education. Report by the New York Committee on the Study of Hospital Internships and Residencies, Jean Alonzo Curran, Secretary. Pp. xxx + 492, New York, The Commonwealth Fund, 1938, cloth, $2.50.

REINDUCED PNEUMOTHORAX

A Case of Bilateral Alternating and Simultaneous Collapse Reëstablished Five Times

J. N. HAYES[1] AND LAWRASON BROWN[2]

In a recent article on reinduction of pneumothorax, Shamaskin and Rogoff (1) reported a case of bilateral pneumothorax in which collapse was successfully reëstablished on both sides. The right lung had been compressed for fifteen months and after an interval of seven months of reëxpansion was again collapsed for eighteen months. The pneumothorax was finally abandoned on account of massive effusion. The first pneumothorax on the left side had been maintained for nine months and after fourteen months of reëxpansion was again established for fourteen months up to the date of reporting. Several very small effusions occurred on both sides during the first bilateral pneumothorax, which was voluntarily abandoned because the lungs were considered healed. This was confirmed from the X-ray films after the lungs had resumed their function. The authors could find no similar case reported.

We report the interesting history of a patient who had alternating therapeutic pneumothorax, three times on the right side and twice on the left. The salient points about the treatment are included in table 1.

Case Report

Pulmonary tuberculosis was first diagnosed in September, 1920, when the patient, a young woman, was 18 years old. She entered the Loomis Sanatorium with a cavity, 6 by 4 cm., in the second interspace and a moderate amount of infiltration from the first to the fourth ribs on the right side. In the left lung was a moderate amount of infiltration near the root and middle third (figure 1).

First artificial pneumothorax: The right lung was collapsed at the Loomis Sanatorium in December, 1920. The treatment was effective, the upper lobe being collapsed 90 per cent and the lower 50 per cent, with closure of cavity. No effusion occurred. The disease increased in the left lung in April, 1922 (figure 2). Refills were discontinued in July, 1922. The lung expanded by September, 1922 and was in good condition.

[1] Saranac Lake, New York.

[2] Deceased.

Interval note: After discharge from the sanatorium she spent eight months in bed at home and two months at Stonywold Sanatorium. She came under our care in June, 1923, complaining of fever and recent blood streaking. A roentgenogram revealed on the right a relatively inactive infiltration of the root and middle third; on the left, infiltration of the upper and middle thirds with a cavity in the apex. She improved generally but the cavity became larger (figure 3).

Second induced pneumothorax: This was begun on the left side on March 21, 1924. The pressure readings were: −2 to −10; 250 cc; −1 to −6. Two small effusions occurred in the sulcus, April to June, 1924, and November, 1926 to January, 1927. The cavity closed slowly although the upper lobe was quite well collapsed. Some adhesions to the apex and to the diaphragm were present. The cavity was finally invisible in March, 1926. In the right lung

TABLE I

SIDE	DATE	AGE OF DISEASE	DEGREE OF COLLAPSE	EFFUSION	DURATION OF COLLAPSE	REASON CEASED	INTERVAL OF EXPANSION TO RECOLLAPSE
		years			*months*		
R.	12/20	2	Effective	None	19	Extension L.	7 years
L.	3/24	6	Effective	Slight, twice	45	Extension R. Healed L.	51 months
R.	6/29	11	Effective	None	39	Healed R. Anoxaemia	1 month
L.	3/32	14	Slowly effective	Slight with reëxpansion	32	Healed L.	
R.	10/32	14	Selective, effective	None	7	Involuntary	

the roentgenogram revealed slight progression of disease in August, 1924 and in February, 1925 when a small cavity was seen. A small haemoptysis occurred in February, 1925. In April and August, 1925, the right lung was better and cavity was not seen on the films, but in December, 1925 a small cavity was again visible in the apex. In March, 1926 and February, 1927, this cavity was difficult to see, but the right upper lobe gradually contracted toward the apex and a definite small cavity was seen in it (figure 4). During this summer the patient worked a little due to her poor circumstances. She had no fever but occasionally had pinkish sputum. She experienced gradual loss of weight from 152 to 142 pounds. Pneumothorax was stopped in October, 1927, as the lung was considered healed. The lower lobe had been maintained under partial collapse. Reëxpansion was complete in January, 1928 (figure 5).

FIG. 1

FIG. 2

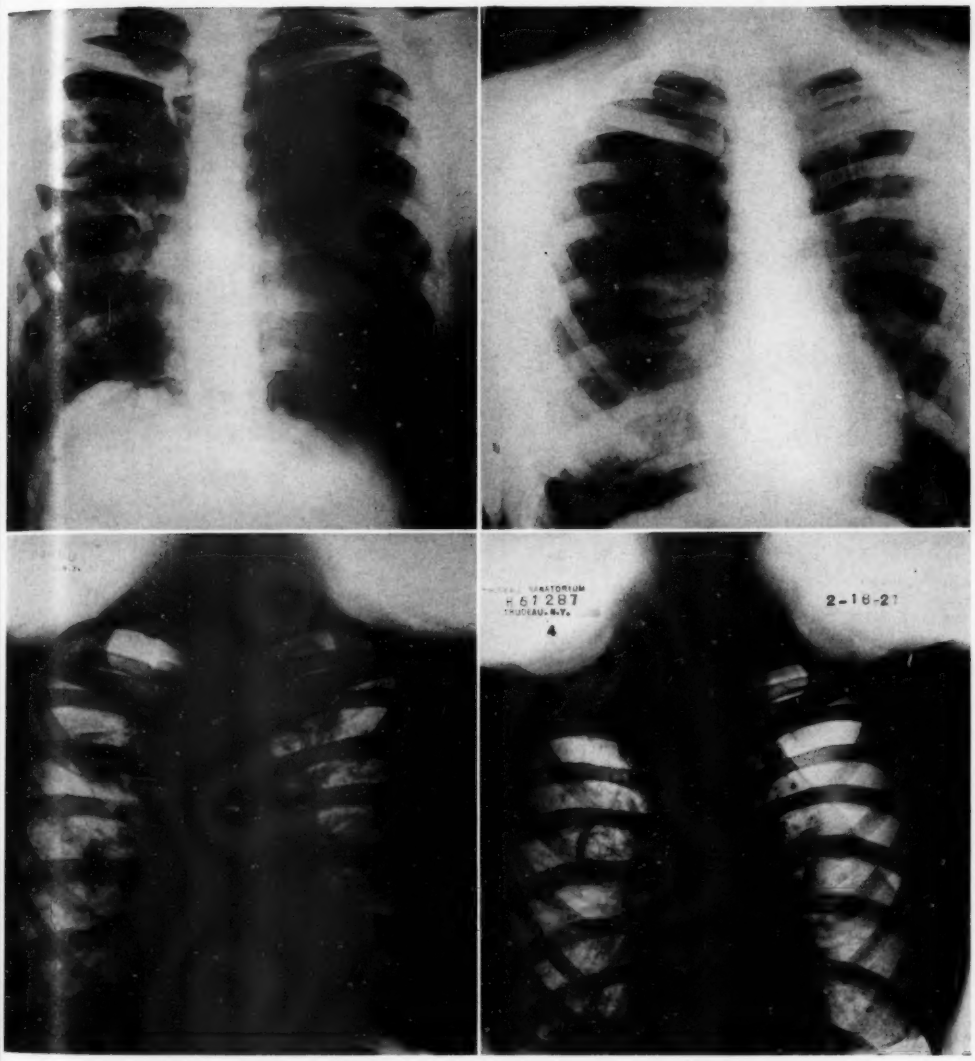


FIG. 3

FIG. 4

FIG. 1. November 24, 1920. Before first pneumothorax on right at Loomis Sanatorium, December, 1920 to July, 1922. Cavity upper right.

FIG. 2. April 12, 1922. (Courtesy of Loomis Sanatorium.) Right: pneumothorax. Left: progressive disease.

FIG. 3. January 4, 1924. Appearance before second pneumothorax on left, March, 1924 to October, 1927. Right lung has reëxpanded. Cavity upper left.

FIG. 4. February 16, 1927. Right: increased disease at apex. Left: cavity closed.

Interval note: Slight fever with blood streaking occurred in late December, 1927. There was a slight increase of disease in the right mid and basal areas in January, 1928. In May increased infiltration was noted in the right upper lobe with two cavities. Less inflammation was present in the lower half. On the left side the tubercles appeared to be calcified. Blood-streaked sputum not infrequently occurred. Cough and expectoration increased. The right lung was better in August and the cavity was hard to see. Cough ceased and expectoration was almost absent. She married. Several therapeutic abortions were performed. She was home from October, 1928 to May, 1929 under poor discipline. A febrile attack set in in May. An X-ray in June, 1929 showed a cavity 4 by 4 cm. at the right apex with relatively "soft" disease to the fourth rib. In the upper third of the left lung were fibrous tubercles, which appeared to be arrested (figure 6).

Third induced pneumothorax: This was begun on the right side on June 14, 1929. The pressure readings were −3 to −8; 300 cc.; −2 to −4. The entry was easy but the pleura was a little thickened. No effusion occurred at any time. In December, 1929, with 65 per cent collapse and the lower lobe under only slight collapse, the cavity was closed (figure 7). Tubercle bacilli were absent then and in March, 1931. She had moderate dyspnoea. A negative pressure on both inspiration and expiration relieved it. The mediastinum was not fixed. Increased cough and expectoration were present in June, 1931. An X-ray film taken in July, 1931 showed on the right effective selective collapse; on the left, a cloud resembling atelectasis at the apex. No fever occurred. Marital difficulties arose. In November, 1931 a questionable cavity was noted at the left apex. In January, 1932 two small cavities formed at the left apex. Physical signs of consolidation and cavity were present here. The right lower lobe was now allowed to reëxpand to the lateral wall to prepare for pneumothorax on the left side (figure 8). Small haemoptyses occurred in January and on February 28 with slight pain over the left apex. Pneumothorax on the right was stopped on May 21, 1932, with the lower lobes well expanded and the upper lobe nicely collapsed. Pneumothorax on the left was begun on March 2, 1932. Marked dyspnoea and anoxaemia present in late May were relieved by aspiration of gas from the left side. Slow reëxpansion of the right upper lobe took place during the summer.

Fourth induced pneumothorax: This was begun on the left side on March 2, 1932. It was successful on the first attempt with collapse present on the right. Initial pressure readings were not recorded, but subsequent readings were negative, for example, −4 to −10. An X-ray taken May 12 revealed the right upper lobe well collapsed, lower lobe expanded; on the left, band adhesions to the cupola, the cavity 2 by 4 cm. and smaller, the lower lobe partially collapsed and adherent to the upper lobe and to the diaphragm. On May 28 we aspirated 300 cc. of gas to relieve the dyspnoea. The patient had

FIG. 5

FIG. 6

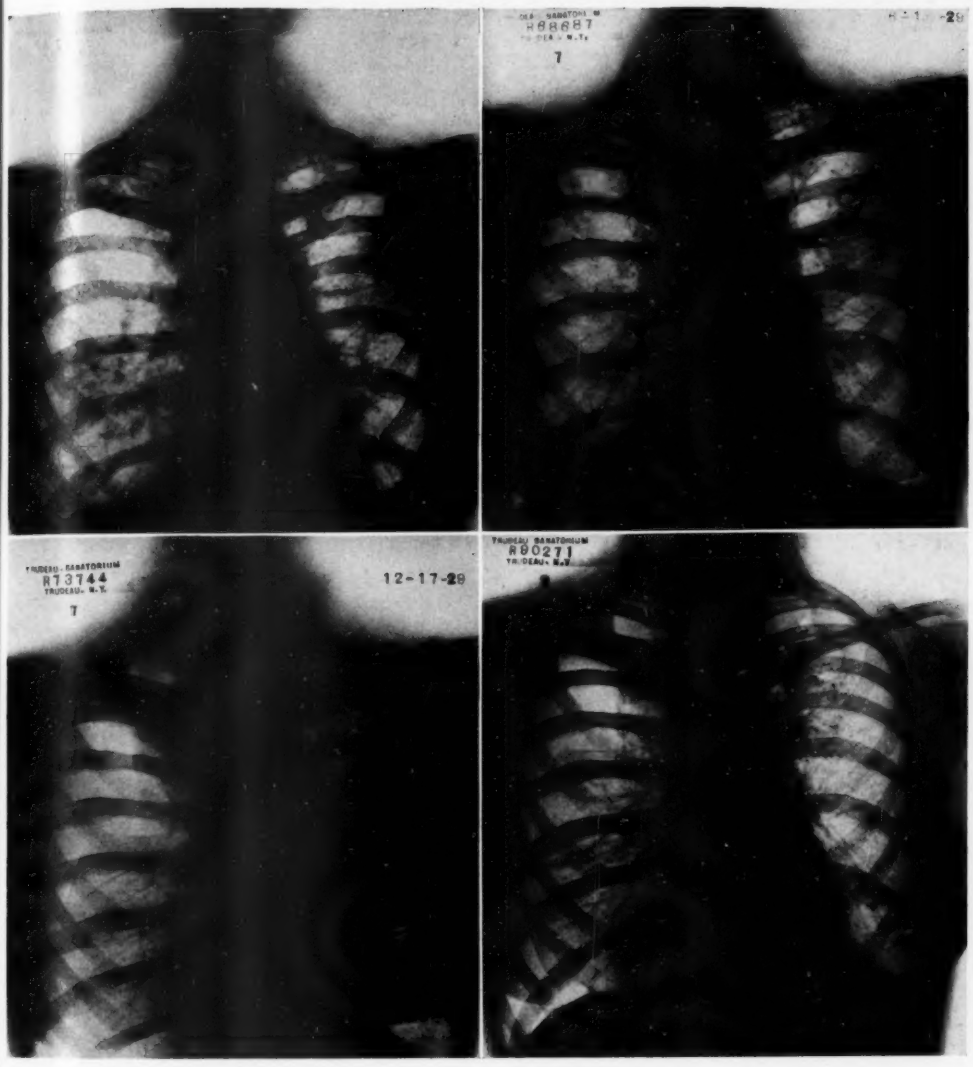


FIG. 7

FIG. 8

FIG. 5. January 13, 1928. After expansion of left lung. Note good fibrosis and calcification.

FIG. 6. June 3, 1929. Before third pneumothorax on right, June, 1929 to May, 1932. Cavity upper right.

FIG. 7. December 17, 1929. Right: pneumothorax, cavity closed. Left: arrested.

FIG. 8. January 13, 1932. Before fourth pneumothorax on left, March, 1932 to March, 1934. Cavity upper left.

been dizzy and faint. She had a pulse rate of 144, slept poorly and had to sit up and lean forward on the table. Her blood-pressure was 110/90 on the right, 100/90 on the left. On May 29 we aspirated 600 cc. gas. This relieved the anoxaemia immediately. On July 14 she had a 30 per cent pneumothorax on the right side and 65 per cent on the left side with an adhesion at the apex holding the cavity open (figure 9). On August 16, 1932, Doctor Welles severed a membranous adhesion partially and two thin strings nearby. The severe dyspnoea was immediately improved (see note about reappearance of cavity and resumption of pneumothorax on the right side in September under "fifth pneumothorax" below). In September the left upper lobe lay in front of the shadow of the spine with the cavity smaller but visible, especially fluoroscopically. The collapse was 65 per cent. The cavity appeared closed in the X-ray film of January, 1934 (figure 11). No refills were made after March 22, 1934. The left upper lobe remained contracted and the lower lobe expanded to fill the pleural space. An apical pneumothorax was seen until October 2, 1934. A very small amount of fluid formed near the base during the expansion.

Fifth induced pneumothorax: This was begun on the right side on October 1, 1932. After stopping the refills in May, 1932, the right upper lobe had slowly reëxpanded. During the last two weeks of September she complained of aching over the right apex and shoulder. On September 25 the pain was severe and she coughed up two large lung stones (one-quarter inch) and three or four little ones of pin-head size. With this she expectorated some thin sputum and after this very little. An X-ray taken on September 28 showed, on the right side, the lung practically completely expanded, a questionable thin gas pocket over the apex and possibly a minimal amount of fluid at the second intercosted space laterad. A cavity, 4 by 2 cm., lay in an area of calcified tubercles in the right upper third; on the left, pneumothorax 65 per cent. The initial pressure was −20; 150 cc.; +8 to −8. The pleura was thick and tense. The needle was introduced at the second intercostal space anteriorly. No effusion occurred during the course. In October there was some collapse of the upper and lower thirds under moderately positive pressure, for example, October 24, +7 −2; 200 cc.; +12 +5. The breathing was not increased in rate after refills on the right side. The cavity closed October 22 (figure 10). It was difficult to enter the apical pocket on May 17, 1933, and no more refills were attempted. The lung reëxpanded in a month's time.

Course to date: After both lungs had reëxpanded the disease in both upper thirds showed calcified tubercles and increasing fibrosis. Shortness of breath ceased after cutting the adhesion on the left. Stopping pneumothorax on the right made no difference in the respiratory rate. The patient had felt that the little sputum came from the left lung. Tubercle bacilli were present until December, 1935, and continuously absent since then.

FIG. 9

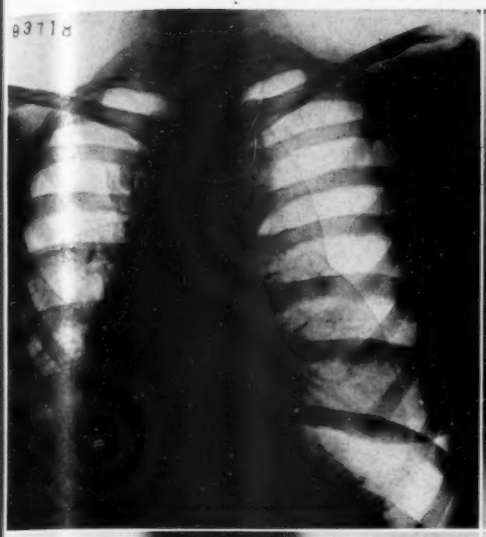
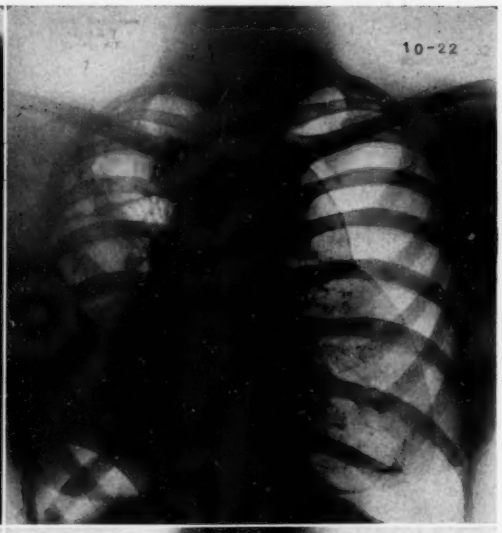
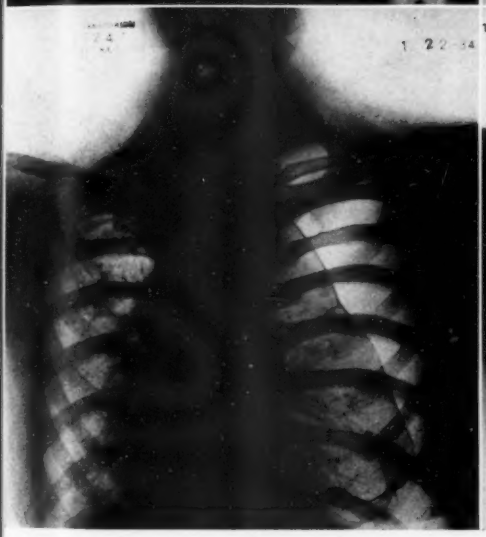


FIG. 10





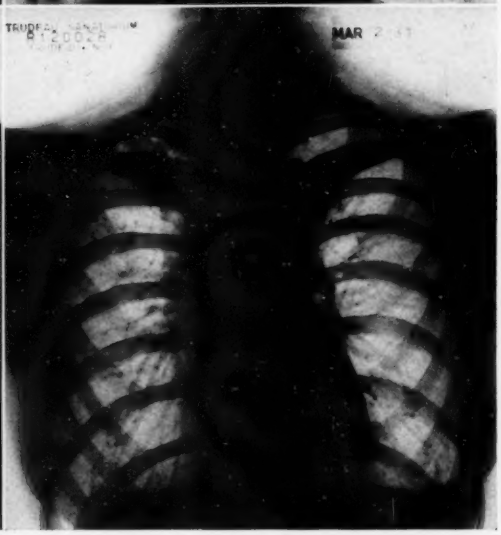


FIG. 11

FIG. 12

FIG. 9. July 14, 1932. Right: expanding. Left: pneumothorax, cavity; before pneumonolysis.

FIG. 10. October 22, 1932. Right lung had expanded in May, 1932. Resumption of pneumothorax, fifth, on right, October, 1932 to May, 1933. This last pneumothorax was instituted when a small cavity reappeared following haemoptysis and coughing up of stones from right lung.

FIG. 11. January 22, 1934. Right: expanded after fifth pneumothorax. Left: fourth pneumothorax, cavity closed.

FIG. 12. March 2, 1937. Both lungs appear healed. Left upper lobe greatly contracted.

A *fistula in ano*, practically inactive for fourteen years, became inflamed in October, 1934, and was operated upon in January, 1935. Slow satisfactory healing followed throughout one year, but the patient lost weight, from 147 to 132 pounds, and was quite weak for many months. During 1936 and 1937 she steadily regained strength and studied typing and stenography. Now she has no cough or expectoration, weighs 139 pounds and feels fine (figure 12).

DISCUSSION

The first two pneumothoraces had not fixed the mediastinum although they had been maintained for nineteen and forty-five months respectively and small effusions had formed during the second collapse, on the left side. With neutral pressures the mediastinum bowed to the left during the third collapse.

During both courses of pneumothorax on the left side, the cavity in the upper lobe closed very slowly. The reëxpansion of this lung after the fourth pneumothorax was very interesting in that the upper lobe remained collapsed and the pleural pocket was filled by the distended lower lobe.

Although the treatments were initiated in alternating or consecutive fashion, the collapse was simultaneously bilateral on two occasions.

When the lung had reëxpanded after each pneumothorax, the disease appeared to be arrested, that is, X-ray evidence of fibrosis and calcification was present. Yet exacerbation occurred in the old sites. The redevelopment of cavity in the right lung before the fifth pneumothorax was quite remarkable because there were numerous calcified spots there. The patient spat up stones and cavity was again visible. On this occasion fixation of the mediastinum and loss of elasticity of the lung were evidenced by the very low initial pressure (-20) and the quick rise to $+8$ to -8 after introducing 150 cc. of air. At this time pneumothorax was present on the left side also.

The fact that the first four pneumothoraces were terminated voluntarily probably facilitated the easy successful induction of the successive collapses. The absence of a large effusion was, no doubt, helpful. On the right side no effusion was ever noted. Without doubt pneumothorax can be successfully reëstablished more frequently than we formerly thought possible. More recently we have been more assiduous in trying to find the pleural pocket in difficult cases. On several occasions with disease in the upper third of the lung we have found a free pleural space near the apex posteriorly, a site we never tried some years ago.

REFERENCE

(1) Shamaskin, A., and Rogoff, J.: Amer. Rev. Tuberc., 1937, *36*, 403.

RESULTS OF COLLAPSE THERAPY IN PULMONARY TUBERCULOSIS[1]

FRED R. HARPER[2]

In recent years surgical procedures have become more widely used in the treatment of pulmonary tuberculosis. Most of the larger tuberculosis centres, as well as many of the smaller sanatoria, throughout the country are at present equipped to handle a collapse therapy program. With this change in the trend of the treatment of tuberculosis it is important that the results of such a program be studied and evaluated. Leslie and Anderson have made a comprehensive study of a large group of patients in which intensive collapse therapy was used.

In this study I am reporting 275 consecutive cases of pulmonary tuberculosis from the Southern Pacific Sanatorium in Tucson. An effort was made to analyze the type of patients, the extent of their disease, the benefit obtained from each of the collapse therapy procedures, as well as the end results of the entire program.

Incidence: Of the 275 patients, 265 were adult males while only 10 were adult females. The ages of these patients varied from 20 to 70 years with the majority being aged from 30 to 50 years. The reason for the predominance of adult male patients is that they were all employees of the Southern Pacific Railroad. They were all given equal care and medical attention.

Race: Two hundred and sixteen were of the white race while 53 were Mexicans or Indians and 6 were Negroes. In a separate communication I have contrasted the type of disease and the results of treatment of whites and Mexicans. The Mexicans were much more prone to have exudative and haematogenous lesions. The results from any type of treatment of the Mexicans, including collapse therapy, were very poor. The inclusion of this large group of Mexicans will alter the results that might be expected from an equal group of white patients.

Duration of disease: The duration of symptoms before the patients entered the Sanatorium was as follows: over one year, 70; approximately one year, 37; less than one year, 168. The short duration of the symp-

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toms in the great majority of cases is of interest in view of the background of these patients. In the first place all of the patients were examined before entering the service of the railroad. Special attention was given to the chest in these examinations, although roentgenograms were not taken. Furthermore the patients were permitted regular examination and medical attention without additional cost. This included the services of a health car which was sent around to examine all employees at regular intervals. Finally, the history of many of the patients was that they had worked at hard labor to within a few weeks of the time they entered the Sanatorium with no symptoms or knowledge of the existing tuberculosis. Even under these circumstances, at first examination the lesions in the majority of the cases were found to be moderately or far advanced. One wonders whether routine roentgenograms at the time of entering the service would have disclosed early lesions in many of these patients, or whether the tuberculosis developed as rapidly as the histories would indicate.

Stage of the tuberculosis: Using the standards of the National Tuberculosis Association, 47 of the cases were classified as minimal, 121 as moderately advanced and 107 as far advanced. These classifications were all made at the time of admission. Regarding the side involved, 181 were bilateral, 48 had right sided involvement and 33 had only left sided lesions.

Type of lesions: There were 52 patients in which the lesions were primarily exudative or haematogenous in character. These lesions were found mostly in the Mexican patients. In 166 patients the lesions were predominantly proliferative, 34 were primarily fibrotic, 4 had pleurisy with effusion on admission and 19 were not classified.

Cavities: There were 164 patients who had cavernous lesions. In 41 of these patients there was bilateral cavitation. In 123 the cavities were unilateral. The location of the cavities in 131 cases was at the apex. In 29 cases the cavities were basal or at both the apex and the base of the lung.

Sputum: The sputum was examined by direct smear once a month while the patients were in the Sanatorium. In cases with persistently negative sputum, all of the sputum was concentrated and examined. In many of the patients with negative sputum the presence of tuberculosis was proved by gastric lavage. In 108 patients the sputum changed from positive to negative as a result of treatment in the Sanatorium. In 75 cases the sputum was absent or negative on admission

and at the time of discharge. In 91 patients the sputum was positive on admission and remained positive.

In the last 36 patients who had negative sputum by direct smear at the time they were being considered for dismissal, the results of a guinea-pig inoculation were obtained before the patient was discharged. It was interesting to find that in 17 of the 36 cases the guinea-pig inoculation confirmed the findings on direct smear, while in 19 cases the guinea pigs were positive although repeated smears had been negative. Pinner has pointed out, and our findings confirm, the value of guinea-pig inoculations and cultures before classifying patients as having negative sputum.

Intercurrent disease: In 145 different patients, diseases other than pulmonary tuberculosis developed and were treated while the patients were in the Sanatorium. In 35 of these patients major operations were performed for conditions other than pulmonary tuberculosis. I feel that this high incidence of intercurrent disease emphasizes the importance of having a well rounded out consulting staff for the Sanatorium as well as adequate hospital equipment to diagnose and treat almost any type of illness. In order to show the importance of being constantly familiar with the patient's general condition, I shall list the various diseases found in this group of 275 patients and the incidence of each.

Tuberculous		*Nontuberculous*	
Tuberculous laryngitis	19	Syphilis	15
Tuberculous enteritis	17	Appendicitis	14
Tuberculous pleurisy with effusion	13	Arthritis	11
Tuberculous empyema	10	Diabetes	10
Tuberculous rectal fistula	4	Hayfever	7
Renal tuberculosis	3	Gonorrhoea	3
Tuberculosis of the spine	2	Cholecystitis	3
Tuberculous epididymitis	2	Duodenal ulcer	3
Tuberculosis of the knee joint	2	Vincent's angina	3
Tuberculous peritonitis	2	Pneumonia	3
Tuberculous meningitis	2	Carcinoma	3
Tuberculous psoas abscess	1	Pneumonoconiosis	2
Tuberculosis of the elbow joint	1	Cardiac lesions	2
Generalized miliary tuberculosis	1	Asthma	2
		Nephritis	1
		Manic depressive psychosis	1
		Mastoiditis	1
		Phlebitis	1

TREATMENT

It was the policy at the Sanatorium to have conferences once a week at which all of the consulting staff members were present. The patients

were reëxamined and X-rayed and laboratory work repeated routinely once in two months at which time they were presented at the conference. By holding these conferences the patients were followed quite closely and the treatment varied to suit the individual patient.

Some form of collapse therapy was used in 69 per cent of the patients. As soon as a particular form of collapse therapy was judged not to be effective another procedure was considered. For that reason many of the patients received several different forms of collapse therapy. Each of the different procedures which were used will be considered and an attempt will be made to evaluate each method.

Bed-rest: Bed-rest and carefully supervised sanatorium regimen was considered to be the most important part of the treatment in all cases. Collapse therapy was used in addition whenever possible, but all patients were treated by bed-rest regardless of the collapse therapy measures which were used in addition.

Bed-rest alone was used in cases with very slight involvement, very far advanced or hopeless cases and patients in whom tuberculosis elsewhere in the body or intercurrent disease definitely contraindicated collapse therapy. There were 87 cases, or 31 per cent of the total, in which bed-rest was the only treatment for the pulmonary tuberculosis. In this group there were 37, or 42 per cent, with minimal lesions. These patients did well and form the majority of the 34 arrested or apparently arrested cases following bed-rest only.

There was a considerable group of Mexican patients with exudative lesions who were classified as moderately advanced on admission. It was our experience that these Mexican patients with exudative lesions did poorly on collapse therapy. Many of these patients were treated by bed-rest only; while some of them improved, many became far advanced and subsequently died.

There were 23 patients, or 26 per cent, who were treated with bed-rest only, who had cavernous lesions. In the majority of these patients the stage of the disease, the age of the patient, or intercurrent disease had contraindicated collapse therapy. These patients constituted many of the deaths from this group. (See table 1.)

Pneumothorax: Pneumothorax was the first procedure attempted in most cases in which it was felt that collapse therapy was indicated. When it was believed that pneumothorax would be needed at some time, it was tried early so as not to allow time to elapse in which the pleurae might become adherent, thus making pneumothorax impossible or of less value at a later time.

TABLE 1

Treatment of pulmonary tuberculosis

METHOD OF TREATMENT	NUMBER OF CASES	TYPE OF LESIONS			LOCATION OF CAVITIES				RESULTS 1-5 YEAR FOLLOW-UP				
		Minimal	Moderately advanced	Far advanced	Unilateral	Bilateral	Apex	Base	Arrested	Apparently arrested	Improved	Not improved	Dead
Bed-rest only	87(31 per cent)	37	23	27	14	9	18	5	29	5	24	6	23
Pneumothorax only	32(11 per cent)	1	14	17	15	6	15	2	2	2	9	3	16
Phrenic nerve interruption only	52(19 per cent)	5	26	21	25	6	22	9	14	9	17	2	10
Pneumothorax and phrenic nerve interruption	51(19 per cent)	2	29	20	31	10	30	11	12	8	20	3	8
Thoracoplasty	30(11 per cent)	0	13	17	22	8	28	2	9	7	6	0	8
Phrenic nerve interruption and scaleniectomy	16(6 per cent)	2	12	2	9	0	9	0	2	6	7	0	1
Oleothorax	6	0	3	3	4	0	4	0	0	2	1	1	2
Intercostal neurectomy	2	0	0	2	0	2	2	0	0	0	1	0	1
Closed intrapleural pneumonolysis	2	0	2	0	2	0	2	0	0	1	1	0	0
Open intrapleural pneumonolysis	1	0	1	0	1	0	1	0	0	1	0	0	0
Total cases	275*	47	121	107	123	41	131	29	68	40	85	15	67
Total percentages		17	44	39	44.7	14.9	47.6	10.4	24.7	14.5	30.9	5.4	24.3†

* Three oleothorax cases and one closed intrapleural pneumonolysis case had thoracoplasty later. They are shown twice in the table but are only counted once in the totals and percentages.

† 42, or 15.3 per cent, died in the Sanatorium; 25 or 9 per cent died after discharge.

Pneumothorax was attempted in 125, or 46 per cent of all cases. In 42 cases pneumothorax was not successful because of pleural adhesions, even though it was attempted early and the patients had a short history of tuberculosis. This experience emphasizes the urgency of attempting pneumothorax as early as possible before the opportunity for its successful induction is lost.

Pneumothorax was used alone in 32, or 17 per cent of the total number of cases. This group consisted for the most part of cases that were moderately or far advanced. A number of Mexicans with exudative lesions were treated with pneumothorax only, because it was felt that pneumothorax was the only collapse therapy procedure indicated in most of these cases. The number of deaths in this group was high because of the Mexican patients and also because other collapse therapy measures were not added in many cases on account of the patients' poor condition. (See table 1.)

Phrenic interruption was combined with pneumothorax in 51, or 19 per cent of the total cases. In a previous report I analyzed these cases in detail. The two procedures were found to be very satisfactory in bilateral lesions; also it was found to be beneficial to add one of the two procedures when the one procedure had brought about improvement but had failed to arrest the tuberculosis. The addition of a phrenic interruption to a pneumothorax often made it unnecessary to perform the more dangerous operation of intrapleural pneumonolysis in cases in which it would ordinarily have been used. Finally, phrenic paralysis was added in most of the cases before abandoning a successful pneumothorax.

Almost all cases in which pneumothorax and phrenic interruption were used together were moderately or far advanced and for the most part cavernous. The results were good, 78 per cent of the group being improved or arrested. (See table 1.)

Bilateral pneumothorax was used either simultaneously or alternating in 12 cases. The use of bilateral pneumothorax has been more popular in recent years since it has been found to be a relatively safe procedure.

Pneumothorax was usually given under relatively low pressure. In 33 cases the pressure was negative. In 69 cases the pressure was positive but with the exception of 4 cases it did not go above +2. While in some cases highly positive pressure is indicated, in most cases a small pneumothorax under negative pressure with frequent refills will accomplish as much as a very extensive collapse, especially if the pneumothorax is selective in its action.

There were 9 cases in which spontaneous pneumothorax occurred. This is almost always a serious and often fatal complication. If death does not occur within the first few hours, empyema frequently results. Three of the nine cases who had spontaneous pneumothorax died, the other six eventually recovered.

Phrenic nerve interruption: Phrenic nerve interruption was done in 137, or 50 per cent of the total number of cases. As mentioned in the previous paragraph, the operation was used frequently in conjunction with pneumothorax. It was also used in conjunction with scaleniectomy, multiple intercostal neurectomy and in some cases before thoracoplasty was resorted to.

There were 52 cases, or 19 per cent of the total, in which phrenic nerve interruption was the only collapse therapy procedure. Many of the cases in which phrenic nerve interruption was used alone were early cases in which this procedure in addition to bed-rest was considered to be adequate. In these cases the results were excellent. Another group of cases were those in which pneumothorax had failed and phrenic nerve interruption was considered the next best procedure. Many of these cases became arrested with only the phrenic nerve interruption. In others, thoracoplasty or other more extensive procedures were used.

In 22 cases in which phrenic nerve interruption was used alone there were cavities at the apex. In 9 there were basal cavities. Contrary to some opinions, I found that phrenic nerve interruption was useful in either apical or basal lesions.

In many of the early cases permanent phrenic exairesis was done before the advantages of temporary phrenic nerve interruption were appreciated. There were 53 cases in which permanent phrenic exairesis was done and 87 in which temporary phrenic nerve interruption was performed. Temporary phrenic nerve interruption should be used in about 95 per cent of cases in which paralysis of the diaphragm is indicated.

Temporary phrenic nerve interruption is less painful and less dangerous. It also has the advantage of being revocable and can be repeated. If properly performed the paralysis lasts only six to eight months and the paralyzed diaphragm therefore does not permanently interfere with other collapse measures at a later date. Furthermore the temporary crushing can be used alternately on either side if indicated.

I pointed out that gastrointestinal symptoms of varying degree follow paralysis of the diaphragm in about 25 per cent of the cases. These

symptoms may last for the duration of the paralysis and after permanent paralysis may be very distressing if not serious.

In order to prevent the temporary paralysis from being too prolonged, the nerve should be handled gently and crushed with a small mosquito forceps. An effort should always be made to identify and divide the accessory phrenic nerves. The average duration of paralysis of the crushed phrenic nerves, whose function was known to have returned, was eight months. The shortest duration was five months. There were 3 cases in which the paralysis lasted over one year and then the function returned. In 14 cases the temporary phrenic crushing was repeated one or more times. In no case was it found impossible to repeat the crushing.

Scaleniectomy: Scaleniectomy is preferable to scaleniotomy. Phrenic nerve paralysis is always used in conjunction with either of the operations. The operations do not have many indications but in our cases were used in thin walled cavities at the apex of the lung. There were 16 cases in which one or the other of the operations was used. While the results were good, I feel that in many of the cases equally good results could have been obtained by using only the phrenic nerve interruption which is a much simpler and less dangerous operation. The one death was an operative mortality, due to injury of the subclavian vein.

Thoracoplasty: Thoracoplasty was done in 30, or 11 per cent of the total cases. All of these patients had cavities. In 22 cases the cavities were unilateral while 8 cases had bilateral cavities. In 28 cases the cavities were located at the apex only, while in 2 cases there were cavities at both the apex and the base. In all cases the lesions were predominantly proliferative or fibrotic. Pneumothorax was carried on for a time or had been attempted in all but one of the 30 patients. In 14 cases the pneumothorax had been carried on for varying lengths of time. Phrenic nerve interruption had been used on the same or opposite side before the thoracoplasty in 17 cases. An anterior thoracoplasty was added to close the cavity in 8 cases. There was no case in which it was necessary to perform a secondary operation or revision. In all but 2 of the patients the modern type of thoracoplasty as described by Alexander was done.

In 4 cases the thoracoplasty was done for tuberculous empyema. Three of these 4 cases had had artificial pneumothorax before the empyema developed, the other one had not. Of the 4 patients in whom thoracoplasty was done for empyema, 2 died.

All of the patients who lived after the thoracoplasty became improved or arrested. There were 8 patients who died after thoracoplasty. While this mortality is too high, there were 3 who died after leaving the Sanatorium. One of these died from a spread to the other lung, in the other 2 cases the cause of death was not definitely known. As mentioned above, two of the deaths were in patients with tuberculous empyema. One patient died from acute dilatation of the stomach following left-sided thoracoplasty and left phrenic nerve paralysis. Thomas and I have reported this complication.

Other collapse therapy procedures: The other collapse therapy procedures which were used included multiple intercostal neurectomy, intrapleural pneumonolysis and oleothorax. Multiple intercostal neurectomy was used in 2 cases. One of the patients had a predominantly exudative type of tuberculosis. The other patient had far advanced cavernous tuberculosis. In the latter case the multiple intercostal neurectomy was done in the hope that the patient's condition would improve sufficiently to warrant thoracoplasty at a later date.

Closed intrapleural pneumonolysis was done in 2 cases and open in one. In many sanatoria intrapleural pneumonolysis is used in a higher percentage of cases. However, the addition of phrenic nerve interruption to pneumothorax accomplished satisfactory results in many cases making the more serious operation of intrapleural pneumonolysis unnecessary.

Oleothorax was used in 6 cases. This procedure was used in some cases of pure tuberculous empyema with active pulmonary tuberculosis. It was also used in several cases in which an effective pneumothorax was being lost due to pleural adhesions. It was not found to be highly successful.

Pleural effusion: Fluid in the pleural cavity is a frequent and often distressing complication of pulmonary tuberculosis. Pinner, Moerke and Saley found tubercle bacilli in 12 of 15 patients in whom pleural effusions complicated pulmonary tuberculosis. Fluid most frequently develops in conjunction with pneumothorax, but pleurisy with effusion in the absence of pneumothorax is not uncommon particularly in haematogenous tuberculosis.

There were 46 patients in this series in whom fluid developed in the pleural cavity. In 31 the fluid was in conjunction with pneumothorax. In 5 the fluid followed an attempted but unsuccessful pneumothorax. In 10 cases the fluid developed before collapse therapy was started.

In 36 patients the fluid was clear while 10 cases had tuberculous empyema. Of the 36 patients with clear fluid, the fluid absorbed without aspiration in 16. The other 20 cases were treated with repeated aspirations with air replacement. Five of the 36 cases were arrested, 7 apparently arrested, 13 improved, 3 unimproved and 8 died.

Of the 10 cases with tuberculous empyema, 4 had pure tuberculous empyema while 6 had mixed pyogenic and tuberculous empyema. The 4 cases with pure tuberculous empyema were treated with aspiration and oleothorax. The 6 cases with mixed pyogenic and tuberculous empyema were treated with thoracotomy and open drainage. In 4 of the empyema patients thoracoplasty was done later. Six of the 10 empyema patients died either in the Sanatorium or within five years after discharge.

RESULTS

The analysis of the results in this group of 275 cases included follow-up records of one to five years from the time of dismissal from the Sanatorium. While the follow-up records were not complete for all of the patients they were particularly accurate in the case of deaths, due to the fact that the Southern Pacific Railroad publishes a monthly bulletin which includes the names of employees who have died.

The results are classified as arrested, apparently arrested, improved, unimproved, or dead. The results of the different types of collapse procedures together with the type of lesions treated are shown in table 1.

There were 68, or 24.7 per cent, arrested; 40, or 14.5 per cent, apparently arrested; 85, or 30.9 per cent, improved; 15, or 5.4 per cent, unimproved; and 67, or 24.3 per cent, dead. Of the 67 who died, 42 died in the Sanatorium while 24 died within five years after being discharged. The reason that only 5.4 per cent are unimproved is explained by the fact that many of the unimproved died after leaving the Sanatorium and are classified as dead.

While the results are not as good as those reported by some of the larger sanatoria in which intensive collapse therapy programs are used, part of the reason for the apparently less favorable results is the longer period of the follow-up records and also because the results include 53 Mexican patients, in which group the mortality rate was 49 per cent. Compared with the report of the National Tuberculosis Association in which 278 sanatoria reported results on 42,107 cases, the results amply justify the intensive collapse therapy program. The National Tuber-

culosis Association report shows only 10 per cent receiving collapse therapy; there were only 17 per cent arrested or apparently arrested, 41 per cent quiescent or improved, 19 per cent unimproved and 23 per cent died.

SUMMARY

The method and results of an intensive collapse therapy program in the treatment of 275 cases of pulmonary tuberculosis are reported. In this group of cases collapse therapy was used in 69 per cent of the patients. Pneumothorax or phrenic nerve interruption or a combination of the two procedures were the most frequently used collapse therapy procedures. The modern type of thoracoplasty was used in cases in which simpler methods had failed to close the cavities. Other less common collapse procedures were used in selected cases when indicated. In 39.3 per cent of the cases the tuberculosis was arrested or apparently arrested, compared with only 17 per cent for the country as a whole where less intensive collapse therapy is used. The results would seem to justify the use of intensive collapse therapy in the treatment of pulmonary tuberculosis.

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ISOLATED FORM OF PULMONARY TUBERCULOSIS[1]

The Experimental Production in Rabbits

CHIEN-LIANG HSU

The isolated form of pulmonary tuberculosis has been recently reported as seen in roentgenograms with the appearance of an isolated, round or oval patch of various density, being usually well circumscribed and clearly contrasted against the surrounding aerated lung. This form of tuberculosis was first described by Assmann (1) and subsequently by Albert (2), Straub (5), Lachmann (4), Bruck (3) and others under various names as "initial tuberculous infiltrate, (Frühinfiltrate)," "round foci type of pulmonary tuberculosis," and "atypical tuberculosis simulating pulmonary metastasis." In view of the fact that the lesion was not always in the initial stage of infection nor was it always round as found in the study made by Wang, Hsu and Wu (6), this type of tuberculous lesion was called the isolated form of pulmonary tuberculosis according to its roentgenological appearance. In trying the various methods of experimental production of pulmonary tuberculosis in animals, the author produced lesions in the lungs of rabbits whose shadows in the roentgenograms simulated the isolated form in human beings. The methods and results are discussed in this presentation.

METHOD AND MATERIAL

Two strains of tubercle bacilli grown on glycerine agar slants were used in the experiments. The strain used for the production of pulmonary lesions was freshly isolated from the sputum of a tuberculous patient. This strain was virulent to guinea pigs. For the injection into the inguinal region, an old strain which was not virulent to guinea pigs was used.

The instrument consisted of a thin-walled glass tube measuring about 3 cm. in length with a caliber of 2 mm. in diameter. One end of the glass tube was beveled in the form of a venepuncture needle. The rest of the instruments amounted to an ordinary dissection set.

Healthy rabbits, 5 to 6 months old, weighing about 1.5 to 2 kilograms

[1] From the Department of Radiology, Peiping Union Medical College, Peiping, China.

were used. Two series of experiments were performed. In one, series A, six rabbits received in addition to the virulent bacilli a subcutaneous injection of 1 cc. of a heavy suspension of avirulent bacilli in physiological saline solution in the right inguinal regional region about three weeks previous to the operation, while in the other, series B, seven rabbits received only virulent tubercle bacilli. By that time, the animals of series A showed a positive tuberculin reaction while those of series B did not respond to the tuberculin test. All the operations were done with aseptic technique under ether by inhalation. Just before the operation, a small amount of the virulent tubercle bacilli was introduced into the beveled end of the glass tube covering a length of column of less than 2 mm., and then blood freshly obtained from a cardiac puncture of the same animal with a small syringe was also introduced into the same end of the glass tube. All of the tubercle bacilli were covered with blood in a column of 2 to 3 mm. A fairly firm clot was formed in about five minutes. The skin of the neck of the animal was shaved and prepared with iodine and alcohol. Under anaesthesia a longitudinal incision of about 3 cm. in length was made in the right side of the neck. After cutting through the fascia and the platysma muscle, the jugular vein was isolated and ligated at its upper portion. Below the ligature a small incision was made in the vein; and, pointing in the direction of the heart, the glass tube containing the clot which had been gently loosened from the wall by means of a probe was inserted into the vein. With a short rubber tube, the glass tube was connected to a 5 cc. syringe containing saline. After the air in the glass and rubber tube was replaced by the saline, the clot was gently forced into the blood-stream followed by 4 or 5 cc. of normal saline. A ligature was applied below the incised wound of the vein. The skin and fascia were closed with silk.

Roentgenograms of anteroposterior and lateral views of the chest of the animals were made at about weekly intervals during the first two months and then at monthly intervals according to the technique described by Greenberg (7) with a film-target distance of 150 cm. In some cases daily roentgenograms were also made. Animals were sacrificed at two, four, ten, twenty, twenty-four and forty weeks after operation in series A and one, two, four, eight, sixteen, twenty-six and thirty-six weeks after operation in series B. The lungs were removed, reinflated, and roentgenograms were again made of the reinflated lungs.

The lungs were fixed in formalin and the lesions were studied macroscopically and microscopically. Microscopical sections of each specimen were stained with haematoxylin and eosin, and acid-fast stain.

RESULTS

All animals developed the same type of lesion in the roentgenograms of the lungs. The lesions were localized, round or oval, well outlined, and homogeneously dense patches, equally distributed in both lungs. In some animals the appearance of the lesions remained stationary throughout the whole course of experimentation, while in others they showed definite increase in size. From the roentgenograms, the smallest lesion measured 4 by 4 mm. in size and the largest one 10 by 11 mm. Two lesions in series A which measured 10 by 11 mm. and 5 by 8 mm. in size underwent cavity formation (figures 1 and 4). There was no secondary reaction in the adjacent lung tissue. Viewed laterally, most of these lesions appear in the posterior part of the lower lung field in the regions of the sixth, seventh and eighth interspace areas; and in the anteroposterior views they usually lay in the medial two-thirds of the lower lung fields, above the diaphragm or partly overshaded by it. Some lesions could be seen in the roentgenograms as early as the sixth day following the operation, but no attempt was made to determine the earliest appearance of every lesion. However, they were all visible two weeks after the operation.

At autopsy, the lesions appeared as solid masses except in two cases where cavities were found. The shadows of the solid lesions in the roentgenograms of the reinflated lungs showed oval, round or rectangular, well outlined homogeneously dense patches. In those with cavities, the shadows of the lesions were also well visualized. The walls were thin except in the upper portions. In one rabbit (figure 1d), the upper portion of the wall of the cavity was thickened and shaped like a crescent; while in the second cavity (figure 4d) the top part was slightly irregular with one large and a few small dense spots.

FIG. 1. Rabbit no. 387 (Series A). (a) Lesion ten weeks old appeared in the form of a patch in the left lower lung field just above the diaphragm. (b) The same lesion appeared in the form of a cavity after the thirteenth week. (c) Posterior location of the cavity in the seventh interspace area. (d) Appearance of the lesion in the reinflated lung.

FIG. 2. Rabbit no. 387. (a) Appearance of the lesion in the cut surface of the lung, (original size). (b) Microphotograph of the same lesion in low magnification, demonstrating the cavity and the caseous mass in the form of a crescent attaching to part of the wall of the cavity.

FIG. 3. Rabbit no. 387. (a) Microphotograph of the lesion in high magnification at the area where the cavity wall is lined with bronchial structure. (b) Microphotograph of the lesion in high magnification at the area where the cavity wall is not lined with bronchial structure.

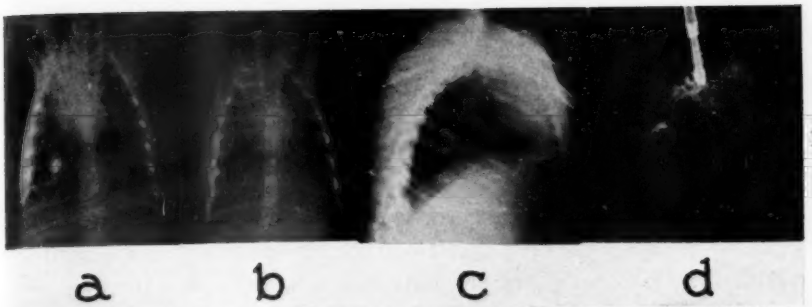

FIG. 1

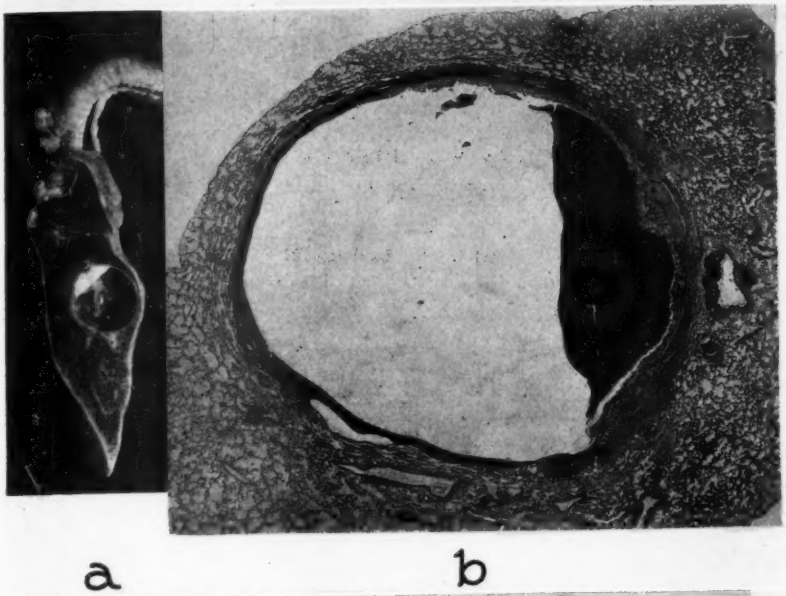

FIG. 2

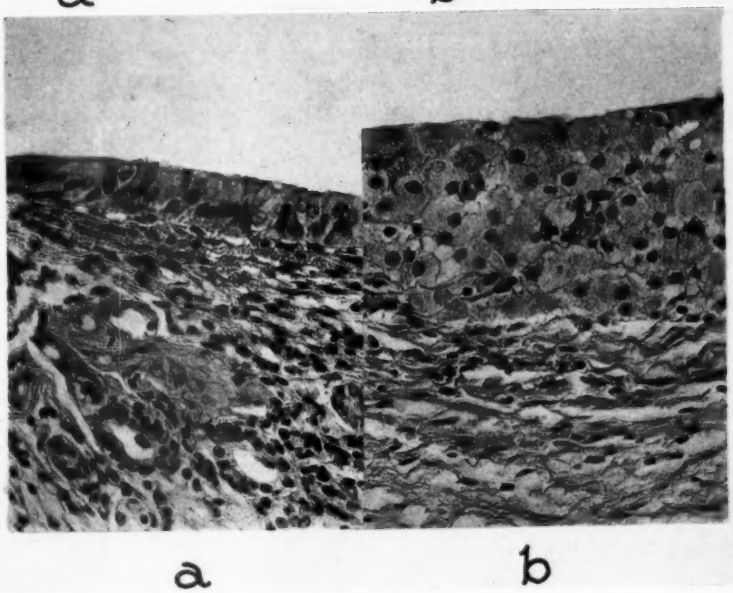

FIG. 3

FIGS. 1–3

There were no definite changes in the pleura and the pleural cavity, and no enlargement of tracheobronchial lymph nodes. The external surface of all the lungs was normal in appearance except that, in rabbit no. 366 of series A, there was a small localized area of dark discoloration in the right lower lobe where the cavity was situated just under the pleura (figure 5). All other lesions were located in the peripheral portion of the lung, being palpable as firm nodules irrespective of the nature of the lesion, whether a solid mass or a cavity. Furthermore there was no gross tuberculous lesion in the other organs of the body.

On section, the cut surface of the solid nodule presented white caseous material surrounded by a capsule. Some black spots were seen in the central parts of two of these caseous masses. The smallest lesion in these specimens measured 2 by 8 mm. and the largest one measured 9 by 9 mm. The surrounding lung tissue was normal. The microscopical sections of these lesions (figures 6 and 8) showed well circumscribed areas of degenerated cells with small dark nuclei or nuclear débris, and indistinct pink cytoplasm. The capsule was composed of much hyalinized fibrous tissue infiltrated by many epithelioid cells and some lymphoid cells. The inner margin of the capsule merged gradually with the degenerated cells. A zone of lymphocytic and eosinophilic infiltration was present on the outer side of the capsule. Tubercles consisting of epithelioid cells and giant cells were seen in the capsular structure of all lesions except in one two-weeks old lesion in series A, one one-week old and one four-week old lesion in series B. Tubercle bacilli were found singly or in groups in the caseous mass in each case. In some cases, the neighboring alveolar sacs were compressed without

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FIG. 4. Rabbit no. 366 (Series A). This animal had two operations, one made on June 12, 1936, and another on August 1, 1936 at an interval of ten weeks. At the time of autopsy, the lesion in the right lung was thirty weeks old and that of the left lung forty weeks old. (a) Lesion four weeks old in the left lower lung after the first operation. (b) Lesion thirty weeks old in the left lung and that 20 weeks old in the right lung. (c) Appearance of the lesions in both lungs before the animal was sacrificed. (d) Appearance of the lesions in the reinflated lungs.

FIG. 5. Rabbit no. 366. (a) Posterior surface of the reinflated lung showing the lesion in the right lung located subpleurally with dark discoloration. (b) Appearance of the cut surface of the cavernous lesion in right lung and the solid one in left lung (original size).

FIG. 6. (a) Microphotograph of the whole lesion in the left lung of rabbit no. 366. Note its relation to the bronchus (low magnification). (b) Microphotograph of the same lesion in high magnification at its capsular region. In the upper portion, the cellular structures in the caseous area are shown; in the middle portion, the capsular area; and in the lower portion, the surrounding pulmonic structures.

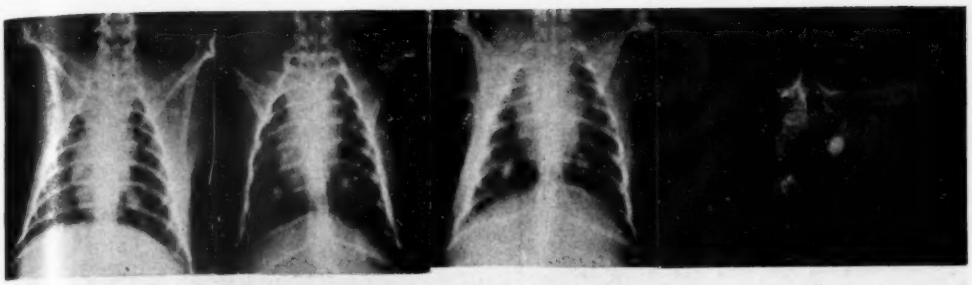

FIG. 4

FIG. 5

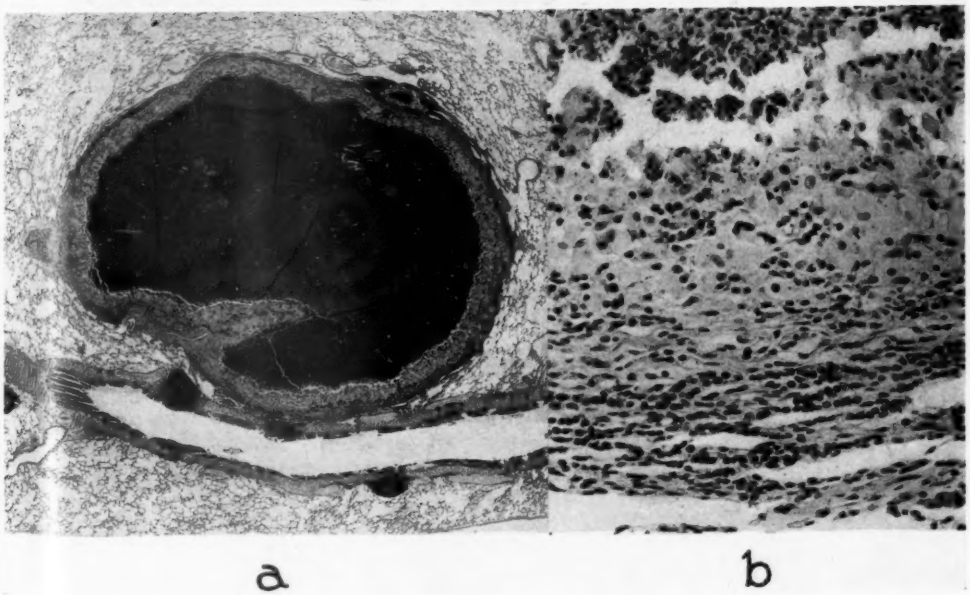

FIG. 6

FIGS. 4–6

cellular infiltration. The main bronchus in all cases except two in series B was found to lie by the side of the caseous areas in intimate association with the capsules.

The cavities, on section, were found to have thin and smooth walls. They contained no fluid. All cavities were well walled off and showed no direct gross communication with the bronchus. Caseous material in the form of a crescent was seen in the upper part of the wall of the cavity in one rabbit (figure 2). The lesion in the right lower lobe in another rabbit (figure 5b) showed two cavities lying side by side, one big and the other small. The smaller one was packed with caseous material which could easily be loosened; and this explained the reason why only one cavity could be visualized in the roentgenogram of the reinflated lung. The walls of the cavities of this rabbit were slightly irregular. Microscopical findings of these cavities were quite alike. They often contained granular necrotic material with tubercle bacilli. A portion of each cavity was lined with columnar epithelium. This suggests a direct connection with the bronchus at one time (figure 3a). In those parts without epithelial covering many phagocytic cells with vacuoles in the cytoplasm were found. Peripheral to the zone of phagocytic cells, there was a zone of infiltration by lymphocytes, plasma cells, eosinophiles and leucocytes. Surrounding this zone of cellular infiltration, fibrosis of moderate degree was present (figure 3b).

DISCUSSION

The lesions experimentally produced in rabbits as described above simulate in some respects the isolated form of pulmonary tuberculosis in man. Roentgenologically the shadows of these lesions in man are homogeneously dense, well circumscribed and clearly contrasted with

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FIG. 7. Rabbit no. 328 (Series B). (a) Lesion thirty-six weeks old in the right lower lung field above the diaphragm. (b) Posterior location of the lesion in the lateral view. (c) Appearance of the lesion in the reinflated lung. (d) Appearance of the lesion in the cut surface of the lung (original size). Note its relation to the bronchus.

FIG. 8. Rabbit no. 328. (a) Microphotograph of the whole lesion with low magnification. Note its relation to the bronchus. (b) Microphotograph of the same lesion at its capsular region with high magnification. The upper portion of this picture demonstrates some cellular structures in the caseous area; the middle portion, the capsular areas and the lower portion, some cellular structures in the surrounding lung.

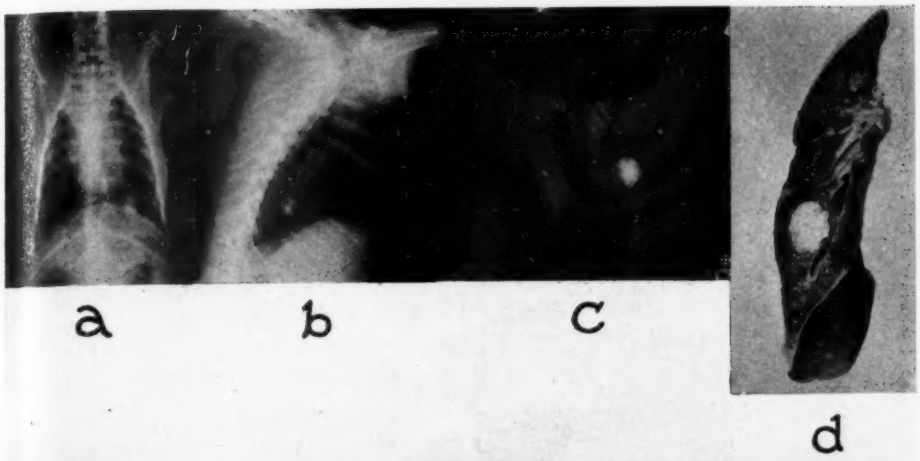

FIG. 7

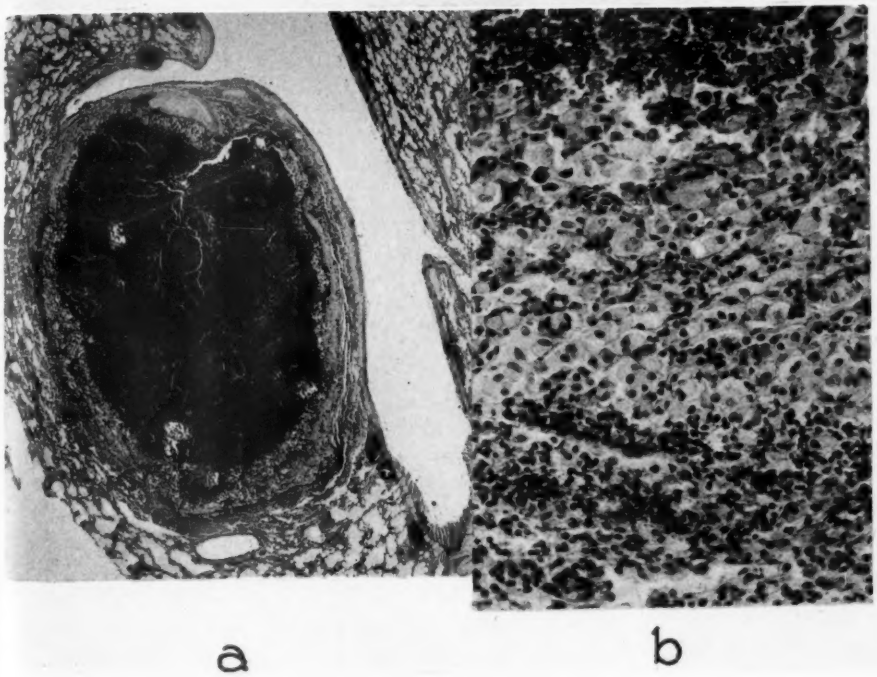

FIG. 8

FIGS. 7, 8

the surrounding lung. They may remain stationary or undergo cavity formation in the course of the disease. The lesions may be located in any part of the lung field but more commonly in the infraclavicular regions (see illustrations of Wang, Hsu and Wu (6)). The shadows of the rabbits' lesions in the roentgenograms were also well localized and sharply outlined, solitary patches which might remain stationary as long as forty weeks or might become cavernous with characteristics as seen in human beings.

Patients with this type of pulmonary tuberculosis rarely come to autopsy and so very few pathological studies of this type of lesions are recorded in the literature. According to Lachman (4), Klein and Wolff (8), and Pagel (9), they were encapsulated caseous foci of diameters varying from a few millimetres to about 2 cm., lying subpleurally and giving no secondary reaction to the adjacent pulmonary tissues. Microscopically, these caseous foci were sharply isolated from the surrounding tissues with fairly thick, hyalinized fibrous capsules. The adjacent alveolar sacs might become atelectatic or emphysematous. Calcification was also visualized in some of the caseous foci. With the exception of two cases in which cavities had developed, all the lesions in the present experiments showed, likewise, caseous masses well surrounded by fibrous capsules, presence of tubercle bacilli, and, in many cases, typical tubercles. Therefore, pathologically, the lesions described in men and in the animals of the experiments are similar in some important respects.

The procedure and the results seem to cast no doubt on the haematogenous origin of this form of pulmonary tuberculosis in rabbits. With the simularities of the roentgenological and pathological findings of this form of lesions in men and in animals, one may assume the haematogenous origin of the isolated form of pulmonary tuberculosis in some of the human cases as resulting from an infected embolus from a distant source.

Klein and Wolff, and Assmann demonstrated connections of these foci with a bronchus and considered them of bronchogenic origin. The results of the present experiment lead one to think that lesions produced by way of the blood-stream may also be located in the immediate neighborhood of the bronchi because normally the branches of the pulmonary artery accompany the branches of the bronchus in the lung (10). The association between the lesions and the bronchi may become even more intimate when the former actually spreads into and erodes the bronchial wall with the discharge of the caseous material into the bronchial lumen

and, subsequently, cavity formation, as in two of the experimental animals.

However, the present experimental data cannot exclude the possibility of bronchogenic origin of this lesion in clinical material. Wang, Hsu and Wu (6) found that three out of fifty cases of this type of pulmonary tuberculosis showed the presence of tubercle bacilli in the sputum. This fact suggests that most of the lesions had no direct communication with the bronchus at the time of examination. The presence of tubercle bacilli in the sputum means connection of the lesion with the bronchus, either by extension and erosion into the bronchus or by bronchogenic origin of the lesion.

It is a general belief that this isolated tuberculous lesion in man is a secondary infection. The preliminary subcutaneous inoculations of avirulent tubercle bacilli into the inguinal regions of the animals were made in order to enable the bacilli later introduced into the lung to produce secondary pulmonary tuberculous lesions as described by Burke (13). With the limited amount of material in the present experiment, it has been found, however, that the lesions of these two series of animals were quite similar except for the formation of cavities in two cases in series A. The formation of cavity only in the sensitized group of animals agrees with the findings of Burke.

The embolic method of producing pulmonary tuberculosis in dogs has been employed by Holman, Chandler and Cooley (14). They used larger emboli which were made of sections of jugular veins of 12 to 16 mm. in length with tubercle bacilli in them. The lesions were produced in the process of anaemia, infarction, caseation, central softening and finally abscess formation. The emboli used in the present experiments were about 2 by 3 mm. in size and consisted of a blood clot containing tubercle bacilli. It seemed that these two different kinds of emboli, as to the size and quality, might produce some difference of reactions of the pulmonary tissue. Blood clot was chosen because its reaction in pulmonary tissue is milder than the reaction of other substances. It is well known that the absorption of a haematoma or the absorption of blood in the lungs of patients with haemoptysis is usually complete and easy. Small emboli were chosen in order to minimize the injury to the lung tissue as a result of vascular obstruction. Karsner and Ash (11), and Steinberg and Mundy (12) have demonstrated that emboli, if small enough, do not cause any infarcation in the lung. This point had been verified in the control experiment. Sterile blood clots of the

same size (2 by 3 mm.) were introduced into the lungs of four rabbits through the jugular vein according to the technique described above. Animals were killed at intervals of one to thirty days after operation. Roentgenograms of the reinflated lungs and sections of the lungs showed no abnormalities. Therefore, it may be concluded that the development of the tuberculous lesions in the present experiment was not due to infarction.

SUMMARY AND CONCLUSIONS

A method for the production of tuberculous lesions in the lungs of rabbits has been described. It consists essentially of the injection of a small blood clot containing tubercle bacilli through the jugular vein. A definite type of pulmonary lesion which was observed at various intervals of from one to forty weeks was constantly produced. Roentgenologically, this lesion gave shadows of localized, isolated patches giving no secondary reaction to the adjacent parenchymatous areas. Pathologically, these animals showed localized lesions well surrounded by fibrous capsules. Tubercles and tubercle bacilli could be demonstrated in them. Attempts were made to correlate these experimental lesions in rabbits to the isolated form of pulmonary tuberculosis seen in the roentgenograms of human beings. These findings may explain the pathogenesis in some cases of the isolated form of pulmonary tuberculosis in man on the basis that the infected embolus originated from a distal source.

The author wishes to express his thanks to Dr. T. T. Wang of the Department of Surgery and Dr. C. H. Hu of the Department of Pathology for reading and criticizing this manuscript.

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THE PATHOGENESIS OF TUBERCULOUS CAVITIES[1]

PAUL M. ANDRUS

A tuberculous cavity is customarily regarded as the "hole" which remains when a corresponding volume of pulmonary tissue has been expectorated. Known destruction and evacuation of tissue is so integral a part of the process of cavitation that this is of course an entirely logical deduction.

The advent of frequent radiography, however, has revealed elements in the "behavior" of cavities, which are, to say the least, puzzling, when explanation is attempted solely on a basis of destruction and organization of tissue. The most outstanding of these difficulties relates to the disappearance of cavities. From serial chest radiographs we now know that spontaneous disappearance of cavities is a frequent and not an occasional event (5, 6, 7, 8, 10, 13, 17). Fales and Beaudet (10) report 47 per cent of all cavities to disappear in this way. We obtained figures of a similar order in a count of one thousand cavities.[3] Such disappearance is in no way characteristically a prolonged and gradual shrinkage but is commonly seen to occur within a few weeks or months. Spectacularly rapid disappearance is repeatedly referred to in the literature (1, 2, 3, 5, 6, 7, 8, 11, 12, 14). It is not too much to say that these observations are entirely unreconcilable with an interpretation of disappearance of cavities by shrinkage of scar tissue only.

The author examined by means of dividers, the changes of size in one thousand cavities in which three or more serial films were available at intervals of from mostly three weeks to three months. We were surprised to find that these cavities were constantly changing in size one way or the other. Many underwent repeated fluctuations in size. Apparently old and thick-walled cavities showed no exception to the rule. It was distinctly rare for a cavity to remain entirely unchanged in size in two consecutive films. The same observations have been re-

[1] From the Mara Laboratories at the Queen Alexandra Sanatorium,[2] London, Ontario, Canada.

[2] Assisted by the National Research Council of Canada.

[3] A correspondingly favorable clinical result is not implied as other cavities very frequently remain patent.

corded by others (5, 7). This too is difficult of explanation, solely on a basis of pathological tissue changes.

All clinicians will, I think, agree that cavity is at least a relatively early feature of tuberculous disease (1, 5, 24). This is particularly emphasized by Fischel (5). No matter how soon one views new and congested infiltrates, associated cavity is rather usually present. Yet if high-grade destruction of tissue is the *sole* element concerned, one might expect cavity to be of less regular occurrence in new disease than is actually the case.

Cavities, when seen to develop, do not regularly commence as tiny holes and undergo progressive enlargement. Much more characteristic is the relatively sudden appearance of fair sized holes. Even very large cavities may appear with spectacular rapidity (3, 5, 11, 12).

Neither is the sudden expectoration of a quantity of exudate a feature of cavity development as is the case in known lung abscess. We have seen cavity appear with apparent complete absence of expectoration, and this is recorded by others (13).

This author is distinctly impressed by inconsistencies between the relations of cavities and their associated disease, if cavities are to be explained as resulting solely from evacuation of tissue. For example we find it difficult to understand how the entirely erratic and unorganized distribution of caseation and softening as seen in radiographs and at autopsy should in itself result in cavities so uniformly spheroidal in form as is actually the case. Irregularly shaped holes would instead seem to be the expected result of this distribution. In viewing chest radiographs we are also impressed by the observation that cavities frequently develop and enlarge rapidly into regions of quite light or trivial disease, and without visible antecedent regional consolidation as one might reasonably expect. Intense consolidation is of course very commonly associated with cavities, but where the process of development is observable, the dense consolidation is much more apt to *follow* than to precede the cavity formation. Cavities may disappear, and then reappear at identically the same position, without the intervening appearance of regional consolidation.

These as well as other considerations suggest that in addition to destruction and organization of tissue, other and further factors are probably important in the formation and healing of cavities.

Such possible further agents we take to be physical forces to which the walls of cavities may be exposed. The literature of recent years

reflects such a concept, but the thoughts are incomplete and controversial. We will therefore attempt a more complete and organized examination of the effects of the various physical forces to which the walls of cavities may conceivably be subjected.

Professor R. L. Allen of the Department of Physics of the University of Western Ontario has very kindly examined this manuscript, and concurs in the correctness of the physical principles outlined.

1. THE DEVELOPMENT OF CAVITIES

As a beginning, let us attempt to trace the possible sequence of events in the formation of a pulmonary cavity. To create a hole or cavity in an organ there must first be an interruption of continuity of tissue. Following such destruction of the supporting elements of a section of lung, cavity may conceivably be created in any one of the following ways: (*a*) by removal of tissue (excavation); (*b*) by dilatation of the resulting potential aperture; and (*c*) by a combination of these two methods.

Let us see then to what forces the limiting surfaces of a discontinuous pulmonary focus may be exposed. The first of these is of course the normal elastic pull of the lung.

As shown in a former publication, the lung is securely anchored by physical forces at all the pleural surfaces, and is constantly stretched in a state of elastic tension in all directions (18). The degree of elastic tension is increased with each inspiratory movement, and may also be altered by various pathological states. Thus it may be grossly increased by pulmonary atelectasis (19) and may be partially or completely relieved by the presence of air or fluid in the pleural space.

Every intrapulmonary air chamber is thus constantly exposed to, and must either resist, or be dilated by, this universally directed outward pull. The normal respiratory air chambers are held patent by this pull at positions of respiratory rest; and are further expanded during inspiration by an increase in the same. If the pull is removed, they collapse by reason of their concentric elasticity.

Warner (23) correctly points out that this force is so directed as to be capable of producing pathological dilatation of bronchi in the presence of sufficient antecedent injury. Unless prevented by counterforces of at least equal magnitude, it is apparent, then, that this elastic pull of the lung must also separate and dilate into a cavity, adjacent surfaces which may become anatomically discontinuous by reason of tuberculous

destruction. The nature and probable effectiveness of such counter-forces, it will be the further purpose of this paper to examine. In the meantime it becomes apparent, as a purely physical proposition, that cavity may be formed in a lung by dilatation of a tear or sectioned surface, and without removal of tissue; that is, it is not necessarily or inevitably an excavation.

Because this elastic pull of the lung is exerted in all possible directions (18), a cavity so formed would in the gross be spheroidal in form. The relative length of the "tearing," and the relative value of the elastic pull in different directions, would determine the shape of such a cavity subject to modification due to localized foci of rigidity or fixation. The diseased tissue would continue to tear at its softest points until the strength of the cavity-wall at the weakest point equalled the value of the pull of the lung. Further weakening of the wall by disease process, or increase in the value of the pull of the lung (as by atelectasis (19)), could by a process of tearing produce sudden further increase in the size of such a cavity, which would be expected to reassume its spheroidal form. Expectoration of destroyed tissue could of course further increase the size of such a chamber.

Changes in the intracavital gas pressure above or below that in the surrounding tissues is a further physical force which might influence the size and form of cavities. The physical basis and probabilities of such gas-pressure changes will be examined fully in further sections of this paper. The elastic pull of the lung is placed first among the dilating forces because of the continuousness and inevitableness of its existence.

Views of Other Authors as to the Effects of Lung Elasticity on Cavities

That the elastic tension of the lung can be expected to exert a spheroidal dilating stress upon cavities has been mentioned by several former observers (3, 5, 11, 14, 15, 20, 27). The traumatizing effect of the inspiratory movements, mentioned by some of these, is of course a part of the same process, consisting of a cyclic increase in the elastic tension of the lung with each inspiration. It is essential to recognize, however, that this "trauma" is not confined to the inspiratory movements, but is continuously exerted even with suspended respiration, and (other than rarely) also when pneumothorax is present.

Coryllos however discounts these opinions, first, because "radiating fibres cannot dilate the cavities unless their ends distal to the cavity were solidly anchored to the chest wall: thus it becomes difficult to

understand how cavities could remain open under pneumothorax, which deprives these fibres of any conceivable support;" and second, because he considers other concomitant physical forces to have been excluded in reaching these conclusions.

The latter of these considerations, which relates chiefly to gas pressure, will be examined in detail in a following section. The former we think to be based upon incorrect physical assumptions. If in the presence of pneumothorax the pulmonary elastic fibres had in fact "no conceivable support," it is apparent that they must contract to a state of nonelastic tension as is actually the case when the thorax is opened. *The persistence of a negative pressure in the pleural space under these conditions is, however, conclusive evidence that the lung is actually stretched in a state of elastic tension.* It follows that the stretched fibres must actually have mechanical anchorage for their termini; also that this tension (other than quantitatively) may hold a cavity open in the same way and for the same reasons as in a closed thorax. The mechanics of this anchorage has been examined in detail in a previous communication (18) and cannot be repeated here. For the present purposes it is sufficient that the proposal that the patency and form of cavities may be a function of the elastic pull of the lung is in no way controverted by the above quoted opinion.

Atelectasis and Cavity Formation

In a previous publication by this author (19) it was shown in detail that pulmonary atelectasis may result in a gross increase in the elastic tension of the remainder of the lung. In the presence of complete destructive discontinuity of tissue such as is known to occur in tuberculosis, a very weak pull may conceivably be sufficient to produce typical spheroidal cavity. An abnormal degree of elastic pull might obviously greatly aggravate this effect. Thus in the presence of atelectasis, larger cavity might occur than would otherwise result from a given injury, or cavity might conceivably be created at positions which would withstand the normal stress.

The literature of recent years has strongly emphasized the frequency and importance of atelectasis as an agent in the development and healing of pneumonitis in general, but especially of tuberculosis. Many references as to this point are given in the above noted study (19). The best evidence of the association of atelectasis and cavity is the very high frequency with which the trachea as well as other adjacent structures

are dislocated to the cavity side. This occurs with a rapidity which precludes organization of scar tissue as a reasonable cause.

We thus conclude that pulmonary atelectasis, though not essential, is in all probability a frequent and highly potent factor in the development of tuberculous cavities. Conversely, a major part of the benefits of pneumothorax must be the lessening of the vicious elastic hypertension of atelectasis (19). Both of these observations are specifically mentioned by Glenn (20).

That atelectasis may also play a major rôle in the closure of cavities will appear in later sections.

Experimental

This hypothesis of the dilatation of pulmonary tears into spheroidal cavities was checked experimentally as follows. A scalpel was inserted into a human lung removed at autopsy. An interior incision was made, the pleural opening tied with string, and the lung inflated through a tube tied in the bronchus. Figure 1 is from an immediately following radiograph. The thin-walled annular high-light was equally visible at the site of the incision, in both anteroposterior and lateral exposures. To prove that these shadows in fact represent a spheroidal hole in the lung, the specimen was frozen (to prevent collapse when opened) and sliced. Figure 2 is a somewhat reduced photograph of two of these slices and shows an obvious spheroidal cavity. The correctness of the physical deducations of the preceding sections are thus experimentally confirmed.

This observation of course does not prove that cavities are not excavations. It does however confirm the soundness of a dilatory hypothesis as an equally reasonable alternative.

Gas Pressure in Cavities

It is next necessary to ascertain whether changes in gas pressure which may arise in cavities are so directed as to be capable of augmenting or inhibiting the inevitable elastic pull of the lung. Patency, shape, enlargement and the disappearance of cavities have each and all in the current literature been considered to be gas-pressure effects (11, 12, 16).

Physical "texture" of cavity walls: Before proceeding however it is essential to point out that although we are accustomed to speak of thin-walled cavities as being "elastic," cavities new or old are not as a class *highly* flexible. To study this point, we radiographed at the

Fig. 1. Roentgenograph of artificial cavity (61 minutes)

Fig. 2. Photograph of artificial cavity (sliced)

end of full inspiration, and again at the end of full expiration, a series of one hundred thin-walled and easily measurable cavities. In only one of these was a difference in size between the cavity in the two films identifiable by comparison with dividers. This single difference occurred in the vertical but not in the lateral plane of the cavity. It may conceivably have been due to a rotation into a new axis and plane of projection, rather than an inspiratory expansion.[4] This immobility is rather to be expected when it is recalled that the margins of cavities, together with a variable amount of surrounding lung, are infiltrated and thus presumably splinted by more or less diseased tissue.

We know however that cavities with great frequency become both larger and smaller over intervals of a few days to a few weeks. This has doubtlessly been an important contributing factor to the general impression of flexibility in cavities. Judging from their behavior as above, together with their textural structure as seen at autopsy, the facts seem to be that cavities are essentially plastic or putty-like in their physical composition and reactions. That is, their walls have sufficient rigidity to resist dislocation by mild and transient changes in tension, but readily yield to a continuance of stresses over hours or days, or to an aggravation of normal stresses. They are not elastic and flexible in terms of short-term mild changes in stresses as are the normal air cells.

With this new concept of the physical characters and reactions of cavity walls, let us examine the expected effects of changes in gas pressure during the respiratory cycle.

The negative pressure of the pleural space and cavities: In the first place it is essential to point out that the patency and spheroidal form of cavities are not the consequence of a lower-than-cavital pressure in the pleural space as stated by Coryllos (16). The detailed reasons for this have been expanded in a former publication (18) and cannot be repeated here. Suffice it that it is there shown that the negative pressure of the pleural space is merely a *pressure guage* registering the value of a remote force, namely, the elastic pull of the lung. To interpret the negative pressure of the pleural space as a primary force causing physical effects upon related structures, is to attribute the rise in pressure in a steam boiler to the upward movement of the needle of the steam-guage; an obviously unsupportable contention, and a confusion of cause with effect.

The loss of sphericity in cavities when the negative pressure of the

[4] This same physical factor may explain the occasionally reported inspiratory reduction in the size of cavities (25), which we find otherwise inexplicable.

pleural space is dissipated at autopsy is also cited by Coryllos as proof of such a causative relationship. Sphericity in cavities and the negative pressure of the pleural space are, of course, in fact due to a common cause, the elastic pull of the lung. *Both* disappear when the elastic tension of the lung is relieved by completely open thorax. They are *common* effects and not cause and effect.

Gas Pressure in Cavities during Respiration

It is next necessary to examine the nature and direction of the gas-pressure changes to which a cavity may be exposed during the respiratory cycle. In a former publication it was shown that the respiratory air chambers are expanded during inspiration by mechanical traction from the outward moving thoracic walls (18). The gas pressure consequently falls, and air flows in from the more rigid bronchial reservoir.

It has been shown above that respiratory changes in the size of cavities are negligible, or at least materially less than that of the remaining aerated lung. If a cavity, in response to the mechanical inspiratory pull, fails to dilate at the same rate as do the surrounding air cells, the intracavital gas pressure will fall less rapidly than does that in the surrounding lung. An outwardly directed gas-pressure difference would be thus set up. Such gas-pressure differences however do not, as might appear at first glance, control the size and form of cavities. Such an interpretation is, as pointed out for the pleural space, a confusion of cause with effects. If a pressure difference is created in this way between the contents of a cavity and its surroundings, *this is prima facie evidence of the insufficiency of such pressure to displace the retaining walls.* If the pressure difference did in fact result in dilatation of the chamber, the pressure would fall and the pressure difference no longer exist.

The physical situation then is simply this. If the cavity walls are sufficiently flexible to be dislocated by a given gas-pressure difference, the walls would be dislocated, not by this gas pressure, but by the antecedent and somewhat greater[5] causative elastic pull of the lung.

During expiration, as shown in a former publication, the elastic contraction of each air chamber causes a rise in pressure in the contained gas[6] (18). Because of the slight or absent contractility of a cavity wall

[5] Greater, because the peak possible values of the gas-pressure difference are lessened by contemporaneous gas flow.

[6] The rise in gas pressure is not (except with cough) caused primarily by pressure from the peripulmonary walls.

the contained gas would not rise in pressure at the same rate as that in the surrounding elastic air cells, and a compressingly directed gas-pressure difference might be deduced. As before, however, such an interpretation would be a confusion of cause with effect. Any compressing effect would be due to elastic contraction of the surrounding lung, and not to resulting gas-pressure changes. *It must be clearly kept in mind, however, that such "compressing" effect is not a positive force, but simply a lessening in the degree of the expanding stress which is constantly present.*

The situation for any isolated portion of a cavity wall is the same as that for the cavity as a whole. If a given region were sufficiently weak to be "pushed out" by an existing gas-pressure difference, the same region would instead be "pulled out" by the antecedent, causative and greater elastic pull of the lung. Thus gas-pressure differences arising from the respiratory movements cannot be formative forces, that is, they do not explain either patency or the customary spheroidal form of cavities. Effects so attributed are in fact the result of a *common* cause, the elastic pull of the lung.

Valvular Obstruction of Cavities

It has been proposed that one-way valves may impede the outflow of air from cavities, while allowing more free inflow, and that raised gas-pressure and dilating and formative effects may result (3, 7, 12, 21). The mechanics of such a valvular mechanism is not described by its proponents. In a former publication we have reviewed the mechanical situation as it relates to bronchial valves (19) and concluded that a one-way valve is not easily or satisfactorily explained. The thing is however entirely possible, and it is necessary to consider the physical results of such a device.

In the first place if we are correct in our observation that respiratory changes of size in cavities are customarily small or negligible, there would be but little expiratory rise in the intracavital gas pressure even if an efficient one-way valve were present. Unless a cavity received as great a proportion of new air during inspiration as did the surrounding air chambers, it would still be exposed to a relative compressional force by the surrounding contracting lung during expiration. Thus a one-way valve would not be expected to be an effective dilating agent even if present.

The chief reason for deducing the existence of a one-way valve under these circumstances is the experimental demonstration of positive gas

pressure in cavities (12, 21). In a following section we will present an entirely satisfactory physical explanation of this phenomenon, so that it becomes unnecessary to deduce a valvular arrangement on this account.

We conclude then that there is no good evidence on which to found a hypothesis of cavity function as a result of one-way valvular obstruction. Also that it is entirely unnecessary to call upon such a device to explain any of the known functions of cavities. In any event unless we concede a one-way valve for each and every cavity, the consideration does not aid us in interpreting the behavior of cavities in general.

Final Conclusions as to the Causes of Patency and Form of Cavities

In the general introduction to this paper it was reviewed that patency, enlargement and the spheroidal form of cavities are not completely or satisfactorily explained solely on a basis of destruction and removal of tissue. It was further shown that respiratory gas-pressure changes do not provide a physically sound explanation of these effects. On the other hand, it is shown that the elastic pull of the lung is so directed as to inevitably dilate into a spheroidal hole the margins of a focus of discontinuity that may arise from destruction. If one reviews and reflects upon the various clinicoanatomical inconsistencies of cavities as outlined in the introductory section to this paper, it will be further seen that each and all of these, insofar as they relate to the patency and form of cavities, become easily and simply understandable in terms of this mechanical dilatory concept. Finally, the correctness of these physical interpretations is proved experimentally by the artificial production of spheroidal cavity under conditions where gas-pressure differences and the removal of tissue are entirely excluded as possible causative agents.

Small multiple cavities in massive caseous disease (Pinner, class 1, (14, 15)) undoubtedly can and do arise by purely excavatory processes. Ulceration into a bronchus may be taken as an essential part of any cavity formation, as otherwise air entry could not occur. The occurrence of tubercle bacilli and elastic fibres in the expectoration of the tuberculous is of course clear evidence that the evacuation of destroyed pulmonary tissue is at least a contributory factor in cavity formation.

From the situation as outlined however, we feel justified in concluding that cavities by and large are much more satisfactorily and logically explained as primarily traumatic artefacts by nature, resulting from the dilatation of destructive tears, rather than solely as "holes" resulting from the removal of a corresponding volume of dead tissue.

2. THE CLOSURE OF CAVITIES

As reviewed in the general introduction to this paper, the frequency and rapidity of spontaneous closure of even large cavities are inexplicable if viewed solely in terms of organization of tissue.

Here also it is necessary to point out that the presence of pneumothorax does not in itself explain the high frequency of prompt closure of cavities under these conditions. Unless, which is unusual, a continuously positive pressure is maintained in the pleural space, a cavity is still exposed to a dilating though reduced force when pneumothorax is present (4). Only with complete relaxation of the radiating pulmonary elastic could the concentric component completely close the cavity as suggested by Pinner (14). As far as pneumothorax is concerned, cavities can be expected to undergo only the same proportion of collapse as does the remainder of the lung. With the usual partial collapse, cavities would then be expected to become reduced in size but not obliterated. This is, however, the reverse of clinical experience, as cavities rather usually disappear "like magic" with partial pneumothorax, unless prevented by adhesions. It therefore becomes necessary to look still further for an explanation of the prompt disappearance of cavities under these conditions.

The Closure of Cavities by Atelectatic Collapse

Until Coryllos presented his hypothesis of the closure of cavities by bronchial blockage and atelectatic collapse (16), no physically sound explanation was forthcoming of the spectacularly rapid closure of even large cavities. This is of course a notable advance. The removal of gas from a chamber by absorption makes possible virtually the full atmospheric pressure as a compressingly directed force. This physical situation should be in no way confused with gas-pressure changes *resulting* from changes in size of a chamber, which we have shown above to be noneffective. In the case of complete bronchial obstruction, either the cavity must collapse, or a "break-through" must occur at one point or another. Salkin and coworkers (9, 13) record the continued patency of cavities and pulmonary lobes, the bronchi to which did not admit the passage of lipiodol. They therefore cast doubts upon the Coryllos hypothesis of closure by bronchial blockage. From the physical standpoint we feel justified in concluding that an air passage must have actually existed somewhere between the chamber and the atmosphere, even though preventing the passage of lipiodol. Otherwise we must

admit the existence of a tissue rigidity sufficient to withstand the full pressure of the atmosphere. We therefore think that the observations of these authors, though most interesting and important, do not controvert the Coryllos hypothesis of the closure of cavities by bronchial blockage.

Admitting the soundness of the Coryllos hypothesis, we feel however that this is not a complete or final explanation of the closure of cavities. Thus it is difficult to understand why bronchi should become so universally obstructed by partial pneumothorax, or even without pneumothorax, as the frequency of disappearance of cavities would in this case indicate. Again, this physical situation explains full patency and full closure of cavities, but, other than for accidental viewings in transitional periods, it does not well account for the continuous fluctuations in the size of cavities recorded above by this author. Thus if during the process of atelectatic shrinkage of a cavity a gas "break-through" should occur, the cavity should more or less promptly return to its original size by reason of the same forces as determined this in the first place. Since cavities respire but little, the size of the air passage should not determine the size of the chamber, as has been stated (7).

Both the fluctuations in size and the closure of cavities are, however, easily explained by a further mechanism which we have nowhere seen mentioned in this connection. This is simply the atelectatic shrinkage of the regional diseased lung during the process of resolution and healing. The high frequency of atelectatic shrinkage of tuberculous lung tissue has been already referred to. The "selective" or disproportionately greater collapse of tuberculous lobes so familiar to the clinician during pneumothorax therapy, can be nothing else than focal atelectasis. Indeed, we would go so far as to maintain that this is probably the chief value of pneumothorax therapy; the "permitting" of atelectasis to proceed selectively in the diseased areas. One has but to view fluoroscopically the vigorous movements of "pneumothorax lungs" to be convinced that "rest" does not explain the benefits of pneumothorax therapy. This selective shrinkage of diseased tissue must "shrink" with it "holes" which may be contained within the mass. That this shrinkage may be quantitatively very great is common knowledge to those familiar with chest films. Its high frequency has been already referred to. Such regional atelectasis might result either from bronchial obstruction, or from bronchiolar obstruction with absorption of intracellular exudate (26). The coincidence of absorption of disease and the disappearance

of cavities is familiar to the phthisiologist and is referred to in the literature (3). In fluctuations of regional atelectasis, we have a sufficient explanation of the fluctuations in the size of cavities as here recorded.

Again, this concept provides us with an entirely satisfactory explanation of the experimentally observed positive gas pressure in cavities (12, 21). If a cavity having an obstructed bronchus is reduced in size by the atelectatic shrinkage of pericavital tissue, such rise in gas pressure is a necessary consequence. This consideration makes it unnecessary to call upon the unsatisfactory valvular concept to explain this phenomenon. From the physical probabilities involved, and the run of anatomicoclinical experiences, it is the author's impression that pericavital atelectatic shrinkage is probably of greater frequency and importance in the closure of cavities than is the bronchial obstruction of Coryllos. Particularly is this the case in the presence of pneumothorax. However there can be no question but that both factors are frequently operative, and doubtlessly often in conjunction. Organization of tissue is of course necessary to complete the repair. Exudation and organization may well complete the closure of small holes.

To avoid confusion it should be mentioned in closing that there is no inconsistency in the concepts here advanced, that atelectasis is a major cause of both the opening and the closing of cavities. The effects will depend upon the "accidents" of time and place. To effect closure of cavity the "shrinking" tissue should essentially surround the "hole" concerned. A cavity marginally or remotely placed in relation to a region of atelectatic shrinkage would, however, be subjected to a dilating stress by this same force. Glenn (20) states: "Cavitation has been present in the upper lobe of all cases that have shown an atelectasis of the lower lobe. In all cases in which lobar atelectasis has developed under our observation, the cavity or cavities in the upper lobe have become larger as the atelectasis becomes more complete." It is a common clinical experience to see one cavity enlarge and another disappear in the same lung or lobe.

SUMMARY AND CONCLUSIONS

1. An examination has been attemped of the various physical and gross pathological forces to which the walls of pulmonary cavities may be exposed.

2. It is shown that destruction and organization of tissue do not completely or satisfactorily explain many of the observed characteristics

of cavities. A logical correlation can be obtained only by calling upon added physical forces as both dilating and constricting agents.

3. From these bases it is concluded that cavities are probably largely traumatic artefacts by nature; that is, they are dilatations of tears in the pulmonary parenchyma. Antecedent destruction of tissue is of course an essential part of the process. Multiple small cavities may undoubtedly arise as a purely excavatory process, but these are not the customary antecedents of the cavities occurring within the manageable range of disease.

4. It is concluded that the customary spheroidal form of cavities is due to the elastic pull of the lung and not to destruction of tissue or to gas pressure.

5. The soundness of the aforegoing deductions is proved by the experimental production of artificial cavity.

6. It is concluded that pulmonary atelectasis which regularly accompanies tuberculous infiltrates is probably a very potent agent in the formation of cavities, by grossly increasing the value of the elastic pull of the lung.

7. The Coryllos hypothesis of the closure of cavities by bronchial blockage and air absorption is fully corroborated as physically sound.

8. It is submitted however that the atelectatic shrinkage of pericavital disease is probably a still more frequent and important cause of the observed shrinkage and disappearance of cavities.

9. It is held that the chief benefit of pneumothorax therapy consists in "permitting" atelectatic shrinkage of diseased lung and cavity to proceed.

10. The term excavation should not be used unless a purely excavatory process is referred to. The term cavitation is essentially more correct for general use.

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EARLY PRIMARY PULMONARY TUBERCULOSIS[1,2]

WILLIAM E. CARROLL

The great majority of children who suffer from primary tuberculosis recover with little or no ill effect. The most frequent course of the disease is well known. After first infection there is a preallergic stage lasting three to eight weeks. After this period the patient becomes sensitive to tuberculin and at this time, in pulmonary localizations, pneumonic-type shadows of parenchymal lesions may be visible on X-ray films. Within a relatively short time the regional lymph nodes become involved and may be sufficiently enlarged to obtrude into the lung field in X-ray films. This parenchymal focus and associated lymphadenitis constitute the primary complex.

In the great majority of cases the primary complex becomes regressive and, after a varying period, heals by fibrous encapsulation and calcification. It usually leaves residual evidence manifested as the characteristic calcified Ghon's focus and as hilar calcification. The majority of patients who achieve calcification remain in good health.

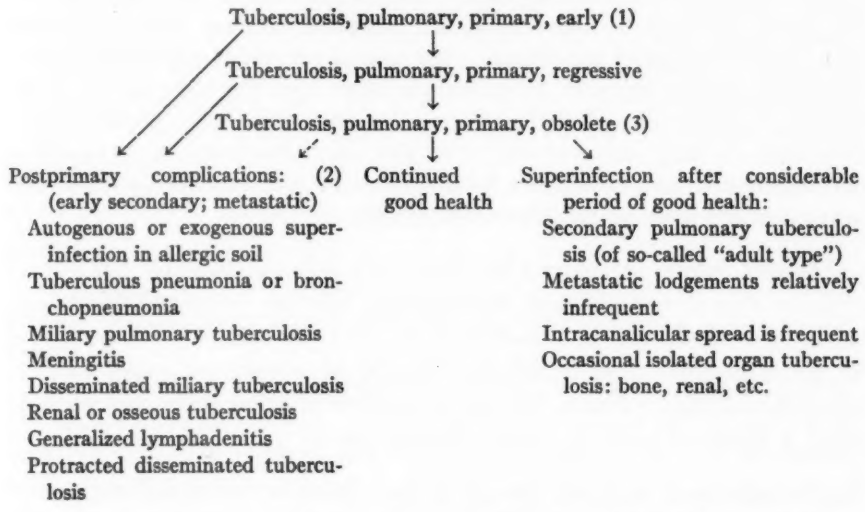
In a certain number of cases the course of disease does not run uneventfully to a fortunate conclusion. At any time, but most often during the early allergic stage, superinfection, either exogenous or endogenous, may supervene and postprimary or secondary lesions of varying sorts may develop. When such manifestations follow the primary lesion closely in point of time we have been inclined to call them postprimary. The commonest postprimary lesions are tuberculous pneumonia or bronchopneumonia, miliary tuberculosis, meningitis, protracted disseminated tuberculosis, generalized adenitis, osseous or renal tuberculosis. Dissemination in such cases usually takes place through the lymph channels or through the blood-stream. The type of disease resulting is fortuitous and depends upon where the bacilli achieve secondary lodgement. When superinfection occurs after a considerable period of good health the resulting lesions have been called secondary. The

[1] Read at the Conference of the Connecticut State Tuberculosis Commission, Meriden, Connecticut, November 15, 1937.

[2] From the Undercliff Sanatorium, Meriden, Connecticut.

most frequent manifestation of late secondary tuberculosis is secondary pulmonary tuberculosis which usually begins as an acute secondary infiltrate. After the acute infiltrate develops recovery may take place or fibro-ulcerative tuberculosis, chronic fibroid tuberculosis, etc., may follow. In late secondary tuberculosis, metastatic lodgements are relatively infrequent. Spread by continuity or by preformed channels is common. This concept is represented schematically in the diagram appended.

SCHEME OF CLASSIFICATION


Tuberculosis, pulmonary, primary, early (1)
Tuberculosis, pulmonary, primary, regressive
Tuberculosis, pulmonary, primary, obsolete (3)
Postprimary complications: (2)
(early secondary; metastatic)
Autogenous or exogenous superinfection in allergic soil
Tuberculous pneumonia or bronchopneumonia
Miliary pulmonary tuberculosis
Meningitis
Disseminated miliary tuberculosis
Renal or osseous tuberculosis
Generalized lymphadenitis
Protracted disseminated tuberculosis
Continued good health
Superinfection after considerable period of good health:
Secondary pulmonary tuberculosis (of so-called "adult type")
Metastatic lodgements relatively infrequent
Intracanalicular spread is frequent
Occasional isolated organ tuberculosis: bone, renal, etc.

Notes: 1. Possibility of multiple contemporaneous sites if implantations take place before allergy develops.

2. Any of these are relatively frequent and follow primary infection closely in point of time. Question of the "progressive primary lesion."

3. In this period, metastatic disease is infrequent but does occur. It is probable that most late secondary pulmonary tuberculosis is due to exogenous superinfection. Endogenous superinfection, however, is not infrequent.

Whether or not there is such a condition as "progressive primary tuberculosis" is controversial; or, perhaps, it is a matter of definition or of point of view. Stewart (1) defines "first infection type" of tuberculosis as the disease produced by an initial infection with tubercle bacilli in any part of the body. He defines "reinfection type" of tuberculosis as the disease produced in any part of the body by reinfection with tubercle bacilli laid down in patients whose bodies harbor foci of primary tuberculosis and whose tissues have been rendered allergic by

a first infection. The term "initial infection" is used as applying to single or multiple implantations of virulent bacilli in nonallergic tissues; whereas the term "reinfection" is employed as applying to single or multiple implantations of bacilli in tissues after their mode of reaction has been altered by an antecedent infection somewhere in the body. In the sense these terms are used the development of tuberculin sensitivity (allergy) is accepted as the dividing line which separates primary infection from superinfection. Stewart (2) further states:

A post-allergic extension or appearance of new tuberculous pathology beyond the limits occupied by the original set of primary lesions marks the onset of a reinfection type of the disease. The time of the initial appearance of new secondary lesions, however, may coincide either with the early allergic stage of primary tuberculosis or with any one of its older, more latent phases. Consequently, miliary tuberculosis, bone and joint involvement, tuberculous meningitis, etc., may complicate the first infection with tubercle bacilli shortly after it is laid down or months or years later.

Stewart, whose experience has been very wide, apparently has a very definite idea as to the line of demarcation between primary tuberculosis and tuberculosis due to superinfection. A tuberculous lesion occurring in an individual already allergic cannot be considered other than a secondary lesion. Pinner (3) and a number of other observers seem to have a different point of view. Pinner states:

In the majority of cases, the primary complex heals in a characteristic manner by fibrous encapsulation and calcification, sometimes by ossification, and leaves a pathognomonic mark. In a certain number of cases the primary lesion is progressive. In a very considerable percentage of progressive cases the direct development of the primary complex leads to death. This last statement is controversial according to the literature in this country where the idea has grown up that primary tuberculosis is never fatal.

A differentiation must be made between the primary complex, which is a morphological entity, and primary tuberculosis, which is a phase of the disease, tuberculosis. It is essentially a matter of definition where to draw the line between primary tuberculosis and the reinfection type of tuberculosis. There is, in reality, no sharp dividing line. In accordance with the best usage in the literature of pathology I would suggest that primary tuberculosis be designated as all the morbid developments which are initiated by the first infection and which progress uninterrupted by phases of healing. On the basis of such a definition, primary tuberculosis is by no means a benign disease. On the contrary, it frequently leads to death.

In another paper Pinner (4) states:

> In the progression of tuberculous lesions is found, probably, the clearest expression of the differences between primary and secondary infections. The functional difference between the two is allergy. Pathogenically the differences are that in the progression of a primary lesion all available routes of propagation of bacilli came into play: lymphatics, blood stream, preformed channels. In secondary infection, dissemination through the lymph and blood stream is quite infrequent, increasingly so with the increase of time elapsed between primary and secondary infection. Progression by continuity and through preformed channels is common in secondary infection. Thus as a characteristic example of progressive disease following more or less closely upon primary infection is seen generalized miliary tuberculosis, frequent in childhood, rare in later life. The characteristic progressive disease of adult life is tuberculosis limited to one organ system, such as pulmonary phthisis, rare in childhood, frequent afterward.

As a matter of specific example it is interesting to note that Stewart quotes miliary tuberculosis as characteristic of tuberculous disease of the reinfection (presumably endogenous) type, whereas, to Pinner, miliary disease is a prime manifestation of progressive primary tuberculosis.

At Undercliff[3] our experience has been in the clinical rather than in the pathological aspects of tuberculosis. During a period of seventeen years about 3,300 children have been under observation. Our conclusions regarding tuberculogenesis are much the same as those reached by Myers, Stewart, *et al.* at Lymanhurst where about 14,000 children have been observed during a period of sixteen years. We hold as a fundamental principle that tuberculous lesions arising in allergic and in nonallergic tissue have vastly different clinical expressions. Before the inception of the primary lesion a person is nonallergic. Within three to eight weeks after initial implantation of tubercle bacilli the individual becomes allergic. It is not impossible to have multiple primary lesions. These are due to multiple contemporaneous implantations before allergy develops. Myers, Harrington, Stewart and Wulf (5) report seven instances of bilateral primary foci among 206 children who presented fresh primary pulmonary tuberculosis. Among 148 cases where primary pulmonary foci were found at autopsy, Blacklock (6) reports fifteen instances of multiple primary foci varying, in individuals, from 2 to 4.

[3] Connecticut State Tuberculosis Sanatorium for Children, Meriden, Connecticut.

Any tuberculous lesion which makes its appearance in any part of the body after the development of allergy and outside of the original parenchymal-adenitic complex is considered a secondary lesion or, if one prefers, a postprimary lesion. This would apply to lesions either close to, or distant from, the primary lesion and would not be influenced by the method of propagation which had been employed. Nor would the time element be of particular significance. If a child died of tuberculous meningitis two months or four years or twelve years after the appearance of a primary pulmonary focus we would consider that he had died of secondary tuberculosis due to meningeal lodgement of tubercle bacilli. By the same token, we would consider that a child who died of tuberculous bronchopneumonia died as a result of secondary pulmonary disease due to lodgement of tubercle bacilli in allergic pulmonary tissue. Miliary tuberculosis is evidence of widespread dissemination of secondary lesions in allergic soil.

We have drawn the line of demarcation at the establishment of allergy because, to our mind, this event marks a definite point of cleavage. Allergic tissue responds to invasion by tubercle bacilli differently than does nonallergic tissue. Destructive and lethal disease follows implantation in allergic tissue. We are inclined to follow Krause's dictum (7) that "acute clinical tuberculosis is always the expression of reinfection in allergic soil."

For the sake of clarity we have expressed our own views as definitely as we can. No disparagement of any other concept is intended. We can easily appreciate that, granting slightly different premises or assuming somewhat different definitions, the idea of primary tuberculosis as a progressive disease is quite comprehensible.

We do not depreciate the potential seriousness of primary pulmonary tuberculosis. This is evident from perusal of table 1. Among 3,300 children 44, or 1.33 per cent, presented lesions due to fresh primary pulmonary tuberculosis. This corresponds closely to the experience at Lymanhurst where out of 14,000 children, 206, or 1.45 per cent, presented lesions of the same type. Thirty-four patients presented no complication on admission. Ten had already developed some type of postprimary disease, 2 patients with tuberculous bronchopneumonia and 8 patients with bone disease. The 2 patients with bronchopneumonia died within a short time. Both of them also had tuberculous cervical adenitis. Twenty-four patients had an uneventful course. Three patients developed tuberculosis of the vertebrae after admission. Six

patients, uncomplicated on admission, died of tuberculous meningitis. Three patients developed frank secondary pulmonary tuberculosis; of these two died, one recovered. One patient had an apparent temporary exacerbation at the site of a primary focus which had become calcified. Of the 44 patients, 10 (22.7 per cent) died; 11 (25 per cent) developed protracted tuberculous disease of bone or joints. These figures would argue that primary tuberculosis is not to be regarded lightly. The relation between tuberculous meningitis and primary pulmonary tuberculosis is very close. In 166 autopsies on cases of tuberculous meningitis

TABLE 1

Results

Total number of patients reviewed	3,300	
Tuberculosis, pulmonary, primary, early	44	
Uncomplicated on admission	34	
Complicated on admission	10	
Tuberculous pneumonia	2	(Died)
Tuberculosis, bone	8	
Tuberculosis, superficial lymph nodes	2	
Uneventful recovery	24	
Developed bone tuberculosis	3	
Died of tuberculous meningitis	6	
Developed secondary pulmonary tuberculosis	3	
Died	2	
Recovered	1	
Apparent temporary exacerbation at cite of primary focus	1	
Total lethal terminations	10	(22.7 per cent)
Total protracted bone disease	11	(25 per cent)

Wallgren (8) found fresh primary pulmonary foci in 82.6 per cent. In 39 additional cases there was X-ray evidence of fresh primary pulmonary tuberculosis in 87.2 per cent. A primary focus is, of course, a necessary precursor of miliary tuberculosis.

No definite information could be obtained concerning the time required for calcification of the primary complex. In the first place, the age of the lesion at the time of admission could not be known. Ten patients died without evidence of calcification; 11 were transferred to the orthopaedic service. On 13 patients films taken every three months were available. Of these, 5 achieved calcification in from six months to

fifteen months after coming under observation. The remainder required varying periods of time ranging from 18 to 39 months.

From the point of view of our clinical experience and in accordance with our concept of tuberculogenesis we have advocated that tuberculosis be divided fundamentally into primary tuberculosis (first infection type) and postprimary or secondary tuberculosis (superinfection type). In order to have a feasible and logical scheme of classification it seems, to us, necessary that the establishment of allergy be regarded as the line of demarcation between primary and secondary disease. We believe that the great majority of children with primary lesions make an uneventful recovery. Otherwise the population of Connecticut, for instance, where 35 per cent of school children are tuberculin sensitive, would be about 500,000 less than the present population. On the other hand, primary tuberculosis is a serious potential menace to any given individual since all clinical types of tuberculosis must, of necessity, be preceded by a primary infection. We have not yet had the courage to allow children with pneumonic-type primary lesions unrestricted activity. We have the hope, at least, that the incidence of lethal or disabling postprimary sequelae may be decreased by careful management during the early phase of primary disease when allergy is high and the liability to metastatic spread is great.

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THE ENVIRONMENTAL FACTOR IN RELATION TO HIGH NEGRO TUBERCULOSIS RATES

RUSSELL B. ROTH

For a great many years students of tuberculosis have been aware that the disease presents different problems in different races. Studies devoted to a delineation and understanding of these problems as applied to the American Negro are numerous, and yet it can scarcely be said that any agreement on the subject has been reached. The fact that the Negro reacts to infection with the tubercle bacillus differently than does the white has been well established and confirmed, principally by four methods of approach. Clinicians have noted that the majority of their Negro patients run a course different from that of their white patients. They have further noticed that certain therapeutic measures bring about different results in the two races. Pathologists have recorded certain general distinctions in the lesions manifested. Statisticians, finally, in exhaustive reports of mortality and morbidity statistics, have found marked differences in rates. In short, there is general agreement that these differences do exist, but in explanation of these differences there is widespread dissention.

The bulk of the best explanations which have been brought forth falls into one or more of four categories which have been outlined in the much quoted work of Pinner and Kasper (1).

1. The Negro, having been in contact with tuberculosis for a much briefer time than the white, has not as yet had an opportunity to acquire the same measure of "inherited immunity."
2. The Negro escapes childhood infection more frequently than the white; therefore an infection acquired later in life occurs in virgin (non-allergic) soil and produces rapidly progressive (more or less) "childhood type" tuberculosis.
3. The apparent differences are due *toto coelo* to environmental conditions and the mental attitude of the Negro in regard to the disease.
4. There exists a true racial (genotypic) difference between the two races (entirely mysterious in character) which confers high resistance on one and low resistance on the other race.

There have, of course, been explanations offered which are not covered in this grouping. There is, also, much recent work on the relation of allergy to immunity which leaves the door open for still another revision of categories. It is sufficient here, however, to point to the third division of Pinner and Kasper's summary and note that environment and mental attitude is held by some to be the entire explanation.

It is indeed unnecessary to dwell at great lengths on the facts concerning the environment of the American Negro. It is notoriously poor from all angles. The principal features of environment as related to tuberculosis are nutrition, housing, frequency of contacts, occupation, personal hygiene, health surveillance and diagnostic facilities, and mental attitude toward the opportunities which are offered for the detection and treatment of the disease. On practically all scores the Negro is at a disadvantage. The poverty of the Negro population as a whole guarantees that the quality and quantity of its diet will be inferior, that it will live in crowded districts in poorly constructed houses with multiple opportunities for the dissemination of the disease from infected to noninfected individuals, and that a large proportion of its wage earners will be employed in industries known to be relatively predisposing to tuberculosis. It is also a truism to note that the Negro is a happy-go-lucky person who is not as profoundly disturbed by the early stages of tuberculous infection as is the average white. Experience has shown that the Negro is reluctant to avail himself of diagnosis and treatment, either through fear or indifference. He is also uneducated in matters of health and personal hygiene, and hence he takes scant measures to prevent the spread of infection. Hence on the basis of these incontrovertible facts many investigators consider that the reason that tuberculosis takes a greater toll among Negroes than whites is clear. They feel that if the conditions among the Negroes were scaled up to those which pertain for the general white population there would be no longer any disparity in morbidity and mortality rates. They feel, therefore, that the problem is essentially one in the province of the sociologist and the educator.

There are statistical surveys which seem to support this thesis. Dublin (2) has offered figures to show that other races living in congested cities show rates no better than those for Negroes. After extensive studies among the white and Negro populations in Tennessee, Smith (3) has concluded that environmental differences are quite adequate to explain the differences noted. A fairly long list of investigators could be brought forth in support of these conclusions. There are, however, several statistical surveys which support a diametrically opposed view. For example,

Green (4) has published figures based on an analysis of the population of Cleveland, Ohio by census tracts. His purpose was to so arrange the population that economically comparable groups could be studied, thus eliminating to some degree the factor of environment, insofar as it is dependent on economic status. His conclusion, after adjusting his figures on mortality rates for difference in age, composition, etc., was that "the colored rate in *each* economic area was 5 times the white rate. The shape of the two (rate) curves was almost identical, that is, both white and colored tuberculosis death rates respond to economic conditions in a like manner." An examination of the available statistics for New York City shows much the same sort of thing. The objection is made, however, that studies of this sort are still open to great sources of error since comparisons must be made with the aid of all manner of mathematical adjustments and artificial divisions of the population.

To overcome partially objections of this sort the present material is offered. It is, of course, impossible to find any groups of Negroes and whites living under conditions that are strictly comparable from the standpoint of environment which are still large enough to have statistical validity. It is felt, however, that the figures from the United States Army offer an opportunity for the study of what amounts to an experiment in equalization of the environmental factor. The figures cover a fifteen year peace-time period. They are made up of the absolute numbers and the rates for tuberculosis morbidity and mortality among enlisted men in the continental United States alone.

It is important to realize the exact nature of the group with which we are dealing. In the first place only males are under enlistment. They are all adults who fall in the age-groups known to be high in the incidence of the disease. All have undergone a physical examination before their enlistment and are therefore presumably in good physical condition at the time of their entrance into the army. Most important of all is the fact that all are living under conditions which can quite accurately be assumed to be identical. To expand this statement a little further, it can be noted that all equipment in the army camps at which these men are stationed is standard. Housing facilities are strictly comparable and the factors of crowding, poor ventilation, inadequate protection against climatic conditions, and improper sanitary conveniences are completely eliminated. The same holds true for nutrition. The rations are the same for whites and Negroes both in quantity and quality. The duties of the men are also similar, hence the occupational element is standardized. The same pertains to diagnostic and therapeutic facilities. The same doctors who

care for the whites also care for the Negroes, the only exception to this being in those camps where there are no enlisted Negroes. Both whites and Negroes are treated in the same hospitals and enjoy the same accommodations. Army routine, of course, demands a fairly high standard of personal hygiene so that it is quite safe to say that the Negroes are not deficient on this score. In general, then, we have eliminated every element which goes to make up environment, and have demonstrated that what differences may be observable cannot be attributed to differences between the environmental conditions of the two races.

While this is generally true it is not strictly true. There are numerous objections which can be raised against a claim for complete parallelism in the two groups. In the first place it is obvious that all of these men have been subject to the factor of environment before admission to the army. The importance of this is minimized, however, by two considerations. In the first place there is the fact that in general the whites who enlist in the army come from the lower economic brackets of the population and have, therefore, been raised in an environment subject to some criticism in its own right. In the second place there is the fact that all enlisted men undergo similar medical examinations. While the medical examination is designed to exclude any men who are physically inferior or are already suffering from a serious disease it is impossible to expect that it can be made sufficiently detailed or extensive to detect all minimal or subclinical tuberculosis from which applicants may be suffering. An illuminating demonstration of this fact has been made in a recent undertaking by one of the X-ray companies working in conjunction with army medical officers. The Civilian Conservation Corps has, for the administration of health matters, been placed under the Surgeon General's office of the United States Army. In 1935 at Camp Dix X-rays were taken of 7,405 men who had been admitted to the Corps, and hence had passed their routine medical examination. All of these plates were interpreted by Col. H. C. Pillsbury with the following results:

CLASS	TOTAL NUMBER	ACTIVE TUBERCULOSIS	PER CENT	? ACTIVE TUBERCULOSIS	PER CENT	INACTIVE TUBERCULOSIS	PER CENT
Under 30:							
White	5,285	38	0.7	50	0.9	277	5.0
Negro	848	7	0.8	6	0.7	33	4.0
Over 35:							
White	1,056	23	2.2	18	1.8	58	5.5
Negro	216	2	0.9	2	0.9	8	3.7

These figures would indicate that a greater percentage of whites pass through the routine examination with tuberculosis than do Negroes. When the above figures are totaled it is found that 7.5 per cent of the whites had tuberculosis which was undiscovered until the X-ray examination was made, while only 5.6 per cent of the Negroes were tuberculous. It would seem then that any error introduced into our figures from this source would tend to enlarge the white rates, and hence would add to, rather than detract from, the validity of the general observations which are to be made.

There are, however, several other sources of error which must be considered because of the effect which they might have on influencing the rates. For example, it is perfectly true that in free time and on "leave of absence" the Negroes return to Negro districts and hence come into more contacts with the disease. This obviously constitutes an uncontrolled factor in our "experimental group." Similarly there are differences in the age distribution of the two races and it is unfortunate that figures for the strengths in the various age groups are not available. Again there is a difference in the average term of enlistment of the white and colored troops, but it is doubtful if this contributes any but an error on the conservative side because the tendency of the Negroes is to stay in the army for longer terms than do the whites. In general it is the policy of the army to hold a man for the full term of his enlistment. Error introduced by death after discharge is thus minimized.

Table 1 presents the figures which have been analyzed. Both absolute numbers and rates are given for morbidity and for mortality. From these figures certain conclusions can be reached. In the first place it is to be noticed that there is a marked lack of fluctuation in the white mortality rates. This implies that the number of whites under consideration is quite ample, so that one or two chance deaths from the disease do not unduly influence the figures in any one year. The same is not entirely true of the Negro rates. There is considerably more fluctuation due to the smaller numbers tabulated. The average strength of the Negro troops over the period studied, however, is 3,810 per year. While it is true that the survey covers only 151 admissions for Negroes with tuberculosis and 58 deaths, certain conclusions seem justified.

It is seen at once that there is a great disparity in the mortality rates. For the fifteen-year period the total white death rate is 0.24 per 1,000 men, while the Negro rate is 0.99, or a ratio very close to 4:1 to the disadvantage of the Negro. Thus it would seem, when this evidence is con-

TABLE 1

*Tuberculosis morbidity and mortality statistics from the United States Army 1922–1936**

YEAR		MORBIDITY			MORTALITY			STRENGTHS
		White	Colored	Total	White	Colored	Total	
1922	Number	241	19	260	22	6	28	W. 91,843
	Rate	2.62	3.98	2.69	0.24	1.26	0.29	C. 4,769
1923	Number	209	16	225	20	4	24	W. 80,537
	Rate	2.60	3.62	2.65	0.25	0.91	0.28	C. 4,418
1924	Number	199	12	211	18	6	24	W. 85,913
	Rate	2.32	2.87	2.34	0.21	1.43	0.27	C. 4,168
1925	Number	208	11	219	19	2	21	W. 85,145
	Rate	2.44	2.78	2.46	0.22	0.51	0.24	C. 3,959
1926	Number	182	18	200	22	5	27	W. 81,904
	Rate	2.22	4.54	2.33	0.27	1.26	0.31	C. 3,965
1927	Number	194	6	200	18	2	20	W. 83,125
	Rate	2.33	1.54	2.30	0.22	0.51	0.23	C. 3,898
1928	Number	184	10	194	31	4	35	W. 83,817
	Rate	2.20	2.51	2.21	0.37	1.00	0.40	C. 3,982
1929	Number	201	5	206	33	4	37	W. 85,769
	Rate	2.34	1.27	2.30	0.38	1.02	0.41	C. 3,924
1930	Number	202	11	213	19	5	24	W. 84,820
	Rate	2.38	2.82	2.40	0.22	1.28	0.27	C. 3,896
1931	Number	152	15	167	22	8	30	W. 82,388
	Rate	1.84	3.99	1.94	0.27	2.13	0.35	C. 3,764
1932	Number	150	8	158	17	4	21	W. 79,761
	Rate	1.88	2.26	1.90	0.21	1.13	0.25	C. 3,545
1933	Number	116	8	124	19	2	21	W. 82,423
	Rate	1.41	2.46	1.45	0.23	0.62	0.25	C. 3,252
1934	Number	132	2	134	18	2	20	W. 83,675
	Rate	1.58	0.67	1.55	0.22	0.67	0.23	C. 2,974
1935	Number	148	7	155	18	2	20	W. 88,745
	Rate	1.67	2.27	1.69	0.20	0.65	0.22	C. 3,090
1936	Number	177	3	180	19	2	21	W. 104,760
	Rate	1.69	0.84	1.66	0.18	0.56	0.19	C. 3,553

* Rates are given per 1,000 men.

sidered in conjunction with other surveys such as that of Green in Cleveland, and in view of the clinical and pathological differences which are to be recognized in the two races, that environment cannot be held to explain the differences in susceptibility to the disease which the two races so generally manifest.

For the sake of completeness it can be noted that, had it been thought advisable to include the years 1920 and 1921 in the survey, the series of cases, in regard to Negro deaths, could have been more than doubled. In 1920 there were 139,153 enlisted whites and 7,764 Negroes. From these strengths there were 150 white deaths from tuberculosis and 54 Negro deaths, giving rates of 1.08 and 6.96 per 1,000 respectively. Hence in that year the Negro rate was 6.44 times the white rate. In 1921 the strengths were 134,058 and 6,303 for whites and Negroes respectively. The numbers of deaths were 50 and 18, and the rates were 0.37 and 2.86 respectively. In this year, then, the Negro death rate was 7.7 times that of the whites. This raises the total number of Negro deaths for the seventeen-year period to 130. These years have been omitted from the general figures given because it is perhaps possible to impute these high rates to a carry-over from wartime conditions.

If this evidence is not striking enough, let us pursue the matter further. The excellent work which has resulted in the establishment of the so called Framingham Standard showed that if diagnostic facilities were used to their best advantage there should be 9 recognized cases of tuberculosis for each annual death due to the disease. It is seen that the average morbidity rate for whites in this study is 2.10 per 1,000. The Negro rate is only 2.56. There is, therefore, only a 4:5 ratio in favor of the whites. Stated in the same terms as the Framingham Standard there are 8.75 recognized white cases per annual white death—a remarkably close approximation to the Standard. On the other hand, there are only 2.63 cases recognized per annual Negro death. Recalling the fact that the same diagnosticians, using the same diagnostic facilities, are handling these cases in both races, this would seem to be a clear demonstration that the tubercle bacillus finds in the Negro a more favorable host than it does in the white, hence the disease follows a more frequently fatal course. If environment is to be called on to explain away the high Negro death rate in the population at large it would seem that one might reasonably expect the morbidity rate of the Negro to be correspondingly higher than that of the white. This remains to be adequately demonstrated. In these army figures this is definitely shown not to be the case. On the

contrary, it seems that we are forced to admit that, whereas the Framingham Standard is quite applicable to the white troops of the army, it is not applicable to the Negro troops, and that environment cannot be blamed for the difference. Since we are dealing with a selected group of men in this study it is not safe to apply our conclusions *in toto* to the population at large, but there is a definite implication that even in civil life the Framingham Standard is not applicable to the Negro.

The fact that tuberculosis, as it is handled by the army, accords so closely to the standard set in the Framingham experiment makes it possible for us to generalize on the rôle which environment does play in tuberculosis in civil life. Evidently diagnosis in the army is quite highly developed, and certainly it will be agreed that treatment is of the best. The average death rate from tuberculosis in all troops combined for this fifteen-year period was 0.28 per 1,000. According to the figures of the National Tuberculosis Association, the national death rate in 1927 for males in the age-group corresponding roughly to that represented in the army (20 to 49 years) was 1.17 per 1,000. A great deal of this difference is undoubtedly due to the fact that we are dealing with a selected group, but certainly we can also hold environment responsible for a considerable part of it. It is obviously, therefore, not the purpose of this paper to minimize the importance of environment as applied to the elimination of the disease as a whole, but simply to point out that even under optimal environmental conditions there would be this same difference in rates. A slightly greater percentage of Negroes might be expected to contract the disease, but a considerably greater percentage of them would die from it.

Grateful acknowledgment is made of assistance and suggestions by Major Charles G. Souder, Dr. Arnold R. Rich and the late Dr. Wade Hampton Frost.

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THE ATTENUATION BY X-RAYS OF THE VIRULENCE OF HUMAN TUBERCLE BACILLI[1,2]

W. F. DREA

This paper summarizes the results of an attempt to change the virulence of human tubercle bacilli by irradiation with X-rays.

X-rays have been used to induce mutations and chromosome changes in all types of germ cells by Muller (1). Similar changes have been produced in somatic cells by Patterson (2). Comparable results in plants have been observed by Stadler (3), Goodspeed and Olson (4), and Gager and Blakeslee (5). Many others have contributed to knowledge concerning this subject.

The basic principles of the chromosomal structures are similar in all living organisms, except possibly the lower fungi and bacteria. It seems probable, however, that the molecules determining hereditary characteristics in bacteria may be affected by X-rays in the same manner as the chromosome molecules.

Rice and Reed (6) have irradiated tubercle bacilli with X-rays in studying the effects of the latter on dissociation. They state that 60 per cent of irradiated R-colony strains and 10 per cent of the controls from a rapidly growing bovine culture showed dissociation toward S forms. The S forms were, however, very unstable to perpetuation. They also report that an S colony secured from an irradiation suspension and carried through for five subcultures, picking out an S colony each time, gave a mixture of R, S and RS colonies in all the transplants. The same was done for another S colony, each subculture suspension being X-rayed and the result was an increasing percentage of S colonies up to 100 per cent for the fifth transplant.

Very nearly all of the X-ray irradiation work done upon bacteria, however, has been concerned with its lethal effects. Duggar (7) has given a good discussion of this subject.

Lange and Fraenkel (8) irradiated cultures of tubercle bacilli and

[1] Presented in part at a session of the Pathological Section at the 33rd annual meeting of the National Tuberculosis Association, Milwaukee, Wisconsin, June 2, 1937.

[2] From the Colorado Foundation for Research in Tuberculosis, Colorado College, Colorado Springs, Colorado.

infected guinea pigs with them. They concluded that only the cultures at least four to five weeks old were killed by exposure to X-rays. Younger cultures from 17 to 20 days were not killed when exposed to the same amount and kind of irradiation. The dose was 10 H.E.D.

Haberland and Klein (9) concluded that X-rays had no direct effect with the technique they used on tubercle bacilli and that the favorable therapeutic effect of X-rays upon tuberculous processes must come as a result of the irradiation of the tissue cells.

Kloverkorn (10) has given brief earlier reviews of similar investigations.

The beneficial effect of irradiation by X-rays upon tuberculous lymph nodes has been known for some time. The doses are too small to kill directly more than a very few tubercle bacilli and it has been generally assumed that the inflammatory tissue cells have been modified in such a way that destruction of the bacilli and healing of the lesion resulted. However, repeated irradiations over a considerable period of time are generally necessary before healing occurs and it seems possible that at least some of the bacilli are thereby attenuated by direct action of the X-rays.

It was anticipated that a long period of time would be necessary to demonstrate any permanent inheritable changes in virulence as a result of irradiation by X-rays of the bacilli *in vitro*.

According to the quantum theory of radiation very numerous quanta of X-rays must be directed toward the bacilli of small volume in order for any single bacillus to be in, or very close to, the path of the moving quantum. Furthermore, the chance of an X-ray quantum being absorbed when passing by or through the bacillus is very slight.

The X-ray quantum used in this work is characterized by its ability to penetrate substances made up of atoms of low atomic number. It also has the property of being able to make an atom emit an electron which is called a photoelectron. This photoelectron starts forth on its career with a velocity determined by the equation $hf = \frac{1}{2}mv^2$, where h is Planck's constant, f is the frequency of the quantum, m is the mass of the photoelectron and v is the maximum possible velocity. This photoelectron, as it moves, knocks off other electrons from the atoms it encounters. It can be shown that since about 35 electron volts are necessary to liberate an electron from an atom there will be produced about 2,850 ion pairs in a very small volume as a result of the absorption of a maximum quantum of X-ray produced by 100,000 volts. The

maximum distance traveled by a 100,000 volt electron in air is about 6.2 cm. Calculated for organic tissue this would correspond to a range of about 0.007,4 cm. Because of deflections in the intense electrostatic fields in the atoms the ionization path must be very irregular and a straight line from the origin to the end of the path is probably 0.001 cm. or less. Most of the photoelectrons liberated will have energies considerably less and it can be assumed that the ionization paths are of the dimensions of the bacilli. It is this intense field of ionization that initiates the biological changes due to X-rays. In addition, the Compton effect, where the X-ray quantum is deflected by collision with an electron, losing some of its momentum in doing so and imparting at the same time kinetic energy to the struck electron, is of biological importance.

The field of ionization due to an X-ray quantum may be wholly or partly within the boundary of the bacillus. If it be assumed that death of the bacillus results if a certain minimum number of ions are produced within its boundary it seems reasonable it will experience some nonlethal change if less than this amount of ionization occurs. Should the X-ray quantum liberate more than this amount of ionization some of it may be produced in the medium outside of the bacillus. This could happen if the fast moving photoelectron started its career outside of the bacillus and then entered it or having started in the bacillus passed through the boundary to the outside. If it be postulated that a "sensitive" volume exists within the bacillus where a certain minimum amount of ionization is necessary for either death or alteration of the cell, the same reasoning indicates how these changes may happen. For general discussions of the physical theories involved and the mathematical treatment the reader is referred to Packard (11), Condon and Terrill (12), Curie (13), and Wyckoff (14).

EXPERIMENTAL METHOD

The investigation was begun on October 13, 1931. The strain chosen for the experiment was H37.

Transplants were made from a culture to a modified Long's medium of pH 7.0; 50 cc. of the media were contained in 125 cc. Erlenmeyer Pyrex glass flasks. Half of the cultures were irradiated; the other half were used as controls.

The flasks to be irradiated were placed above a Coolidge Universal type of X-ray tube immersed in transformer oil. About 1 cm. thickness

of oil, 0.25 cm. of cardboard, the bottom of the Erlenmeyer flask and 2 cm. depth of the media served as filters for the X-rays.

The current passed through the X-ray tube was 3 ma. at 105 k.v.p. The distance from the X-ray tube target to the bacteria was 19.5 cm.

The cultures were irradiated for from 0.5 to 1.5 hours every day with comparatively few exceptions. Every three to four weeks transplants were made to fresh media. At this time the growth of the nonirradiated cultures was profuse and that of the irradiated cultures was less than one-tenth of the controls. Between times of irradiation, the cultures were kept in the incubator at 37.5°C. Except for irradiation the non-irradiated control cultures were treated in the same manner as were the irradiated cultures, being removed to the X-ray laboratory nearby, shielded by lead from the X-rays and returned to the incubator at the same time with the irradiated cultures. Previous to the past year, intensity measurements of the X-ray beam were not made. Since then the intensity was measured by means of an ionization chamber and was found to be 1,872 r units per hour.[3] It is assumed that the same intensity of X-rays was used previously, as the same tube and technique were employed. Through such a long period of intermittent irradiations it seemed very probable that many of the bacilli finally surviving would have had one or more ancestors influenced by the X-rays.

It was determined that the irradiation did not alter the pH or growth promoting property of the synthetic media.

At various time intervals tests of virulence have been made. This was done for the cultures as a whole and for strains developed from colonies presumably grown from single bacilli.

Before virulence tests were done transplants to fresh synthetic media were made two or more successive times with no more irradiation in order to ensure that no bacilli killed by direct irradiation were used in the tests. As stated before the nonirradiated cultures were always treated in the same manner as were the X-rayed cultures. The bacilli injected were always from growths 21 to 26 days old. Aseptic technique throughout this work is emphasized.

Test Group 1

Bacilli irradiated for a total of 336 hours (628,992 r units).

A small amount of growth was removed from the periphery of the

[3] The X-ray dosimeter was loaned by the National Research Council.

culture, dried between absorbent papers, ground in a mortar and gradually suspended in 0.9 per cent sodium chloride. This was filtered through C. S. &. S. no. 589 paper. The bacilli were counted in a Petroff-Hauser chamber.

Two guinea pigs were injected subcutaneously in the right groin with 10^6 bacilli in 1 cc. saline from the descendants of the irradiated bacilli, and two were similarly infected with nonirradiated bacilli. Four weeks later the animals were killed.

The results are recorded in table 1.

The animals infected with the irradiation bacilli had less extensive visceral tuberculosis than those infected with the nonirradiated bacilli.

Attenuation of virulence was indicated as probable in the descendants of the irradiated bacilli.

TABLE 1

	10^6 BACILLI INJECTED SUBCUTANEOUSLY			
	Nonirradiated controls		Irradiated—irradiation 336 hours (628,992 r units)	
Animal number	1	2	3	4
Survival days	28k	28k	28k	28k
Macroscopical tuberculosis:				
Right inguinal node	+++	+++	++	++
Spleen	++	++	+	+
Liver	+	++	+	+
Lungs	−	−	−	−

k = killed

Test Group 2

For test group 2 the descendents of the bacilli reported in test group 1 were used, these bacilli having been irradiated for an additional 100 hours, making a total irradiation time of 436 hours (816,192 r units).

Six guinea pigs were infected subcutaneously in the right groin with 1.2×10^6 bacilli in 1 cc. of 0.9 per cent sodium chloride of the nonirradiated descendants of the irradiated bacilli.

Another group of six guinea pigs were infected similarly with the same dose of the descendants of the nonirradiated bacilli.

The results are shown in table 2.

For $n = (N_1 - 1) + (N_2 - 1) = 10$, t will exceed a value of 3.169 solely by chance only once in a hundred times. For further information concerning statistical treatment consult Davenport and Ekas (15).

The results are statistically significant. Two of the animals killed at the end of 624 days had only slight or no enlargement of their spleens, moderate enlargement of the right inguinal glands, and would have lived,

TABLE 2

	10^8 BACILLI INJECTED SUBCUTANEOUSLY											
	Nonirradiated controls						Irradiated—irradiation 436 hours (816,192 r units)					
Animal number...	1	2	3	4	5	6	7	8	9	10	11	12
Survival days..	61	76	108	155	195	251	148	448	499	537	624[k]	624[k]
Macroscopical tuberculosis:												
Right inguinal node..	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
Spleen..	++++	++++	++++	++++	++++	++++	++++	++++	++++	+++	+	+
Liver...	+++	+++	+++	+++	+++	+++	++	++	+++	++	−	−
Lungs..	+++	+++	+++	+++	+++	+++	++	+	++	++	?	−
	M_c = 141 days s_c = 73.3						M_{xr} = 480 days s_{xr} = 176.8					

k = killed
M_c = mean survival days for control group
M_{xr} = mean survival days for X-ray group
s_c = corrected standard deviation for control group
s_{xr} = corrected standard deviation for X-ray group
s_d = corrected standard deviation for the difference of the means
N_1 = number of animals in control group
N_2 = number of animals in X-ray group
x = survival days for any one of control group
x′ = survival days for any one of X-ray group

$$s_d = \sqrt{\frac{\sum(x - M_c)^2 + \sum(x' - M_{xr})^2}{(N_1 - 1) + (N_2 - 1)}} = 135.3$$

$$t = \frac{1}{s_d} \cdot \frac{M_{xr} - M_c}{\sqrt{1/N_1 + 1/N_2}} = 4.39$$

most probably, for an appreciable time longer as they were in good condition.

A significant fact is the wide variability in the durations of life and this will be evident in all of the work here reported.

Test Group 3

This experiment was a repetition of that of group 2.

The bacilli were transplanted six more times to synthetic media without additional irradiation. The total number of hours of irradiation therefore was the same as for group 2. The last time of irradiation was on August 27, 1933, and the date of infection was on April 8, 1934. The nonirradiated bacilli were transplanted at the same time.

The purpose of this observation was to determine whether or not attenuation of virulence still persisted in the descendents of the irradiated bacilli whose ancestors had not been X-rayed for the previous seven months and twelve days.

TABLE 3

	10^6 BACILLI INJECTED SUBCUTANEOUSLY											
	Nonirradiated controls						Irradiated—irradiation same as for table 2. No irradiation for over 7 months					
Animal number	1	2	3	4	5	6	7	8	9	10	11	12
Survival days	77	98	112	133	143	402	126	382	473[k]	473[k]	473[k]	473[k]
Macroscopical tuberculosis:												
Right inguinal node	++	+++	+++	++	++	+++	++	+	++	+++	+	++
Spleen	+++	++++	+++	++++	+++	++++	+++	+++	+++	−	−	++++
Liver	++	+++	+	++	++	+++	+++	−	−	−	−	+
Lungs	++	+++	++	+	++	++	+++	−	+	−	?	−
	M_0 = 160.8 days						M_{xr} = 400 days					

k = killed

The results are recorded in table 3.

The four animals killed of the irradiation series were in very good condition and might have lived a considerable time longer.

Attenuation of virulence in the descendents of the irradiated bacilli has persisted though there had been no irradiation for more than seven months previously.

Test Group 4

The bacilli to be tested were descended from those irradiated for a total of 556 hours (1,040,832 r units). Injections were made subcutaneously. The dose was 10^6 bacilli in 1 cc. of 0.9 per cent sodium chloride.

The purpose of this experiment was to determine whether the virulence was still further attenuated by continued irradiation.

The results are recorded in table 4.

All of the animals in the group infected by the descendants of the irradiated bacilli were in very good condition when killed. Tissues from each of the spleens from the X-ray group were examined histologically and five did not show any tuberculosis. Two of the right inguinal nodes showed considerable fibrosis under the microscope, indicating healing. Number 7 had no detectable right inguinal node present.

The virulence of the descendants of the irradiated bacilli was more attenuated following 120 hours additional irradiation.

TABLE 4

	10^6 BACILLI INJECTED SUBCUTANEOUSLY											
	Nonirradiated controls						Irradiated—irradiation 556 hours (1,040,832 r units)					
Animal number	1	2	3	4	5	6	7	8	9	10	11	12
Survival days	56	124	131	149	189	237	327^k	327^k	327^k	327^k	327^k	327^k
Macroscopical tuberculosis:												
Right inguinal node	++++	++++	++++	+++	+++	+++	−	++	++	+++	++++	++
Spleen	++	++++	++++	++++	+++	++++	−	−	+++	−	−	−
Liver	+	++++	++++	++++	+++	++++	−	−	−	−	−	−
Lung	?	+++	+++	++	++	+++	−	−	−	−	−	−
	$M_e = 147.6$						$M_{xr} = 327$					

k = killed

Test Group 5

An infecting dose of 10^7 bacilli was used, thereby multiplying the previous doses by ten. Sixty-two additional hours of X-ray for a total of 618 hours (1,156,896 r units) had been given. The technique was as before.

The purpose of this test was to determine the reactions to increased doses of the control and irradiation bacilli.

The results are recorded in table 5.

Five of the six in the irradiation group were in good condition when killed and one was in poor condition.

Increasing the dose shortened the lives of the control group and produced more extensive tuberculosis of the irradiation group.

Attenuation of virulence in the irradiation group was pronounced.

Test Group 6

The bacilli had been irradiated for 897 hours (1,679,184 r units); 279 hours additional since test group 5.

The infecting dose was 8.86×10^6 bacilli in one cc. of 0.9 per cent

TABLE 5

	10^7 BACILLI INJECTED SUBCUTANEOUSLY											
	Nonirradiated controls						Irradiated—irradiation 618 hours (1,156,896 r units)					
Animal number	1	2	3	4	5	6	7	8	9	10	11	12
Survival days	51	62	107	130	132	157	311[k]	311[k]	311[k]	311[k]	311[k]	311[k]
Macroscopical tuberculosis:												
Right inguinal node	+++	++++	+++	+++	++++	+++	++	++	++	++	++	++
Spleen	++	+++	++++	++++	++++	++++	−	+	+++	+++	−	+++
Liver	+++	−	++++	++++	++++	++++	−	−	+	−	−	?
Lungs	+	++	+++	++++	++++	++++	−	−	+	?	−	+
	$M_c = 106.5$						$M_{xr} = 311$					

k = killed

TABLE 6

	$8.86 \cdot 10^6$ BACILLI INJECTED SUBCUTANEOUSLY											
	Nonirradiated controls						Irradiated—irradiation 897 hours (1,679,184 r units)					
Animal number	1	2	3	4	5	6	7	8	9	10	11	12
Survival days	88	89	110	112	119	138	60	178[k]	178[k]	178[k]	178[k]	178[k]
Macroscopical tuberculosis:												
Right inguinal node	++	+++	+++	+++	+++	+++	+++	++	++	++	++	+++
Spleen	++++	++++	++++	++++	++++	++++	+++	+++	+	++++	++++	+++
Liver	+++	+++	++++	+++	+++	++++	+++	−	−	?	−	+++
Lung	++	+	++	+	++	+++	++	−	−	−	−	−
	$M_c = 109.3$						$M_{xr} = 158.3$					

k = killed

sodium chloride and the injection was made subcutaneously in the right groin.

The same suspension of bacilli was used in group 6 as was used in the following group except that this suspension was diluted to one-tenth of that used for group 7.

The purpose of the test was to determine the effect of increased irradiation and to compare the results when two different doses from the same original suspension of bacilli were used.

The results are recorded in tables 6 and 7.

Test Group 7

Conditions and date of infection were the same as for test group 6 except that 88.6×10^6 bacilli comprised the infecting dose.

The purpose of the test was to determine the effects of a still further increase of the infecting dose of bacilli.

The results are recorded in table 7.

TABLE 7

	$88.6 \cdot 10^6$ BACILLI INJECTED SUBCUTANEOUSLY											
	Nonirradiated controls						Irradiated—irradiation same as for table 6					
Animal number.....	1	2	3	4	5	6	7	8	9	10	11	12
Survival days.....	45	53	58	70	77	102	117	174	178[k]	178[k]	178[k]	178[k]
Macroscopical tuberculosis:												
Right inguinal node.....	+++	++++	+++	+++	++++	+++	++++	+++	++	++	++	+++
Spleen.....	++++	++++	++++	++++	++++	++++	++++	++++	++	+	++	++++
Liver.....	++++	++++	++++	++++	++++	++++	−	++	−	−	−	++
Lungs.....	+++	+++	+++	+++	+++	+++	−	−	−	−	−	−
	$M_0 = 67.5$						$M_{XII} = 167.1$					

k = killed

Attenuation of the irradiated bacilli is evident. It is interesting to note the short duration of life of one of the irradiated group 6. The variable responses of the infected animals to the same doses of bacilli from the same suspensions indicate large differences of susceptibility to infection with human tubercle bacilli. Every precaution was always taken to minimize errors of technique.

TESTS OF VIRULENCE FROM STRAINS DEVELOPED FROM COLONIES

Colony Strain Experiment 1

Because the cultures most probably contained bacilli of varying degrees of virulence, it was decided to test for virulence subcultures grown from

colonies which had developed from single bacilli, if such is possible with the technique employed.

This procedure also made it possible to decide on the relative numbers of R, S and I colonies associated with the virulent nonirradiated and the attenuated irradiated cultures.

Masses of the bacilli were removed from the surfaces of the synthetic media supporting the cultures previously tested for virulence. The growths were of 23 days' duration. They were pressed between absorbent filter papers in order to remove the excess moisture. They were then ground in a mortar and 0.9 per cent sodium chloride solution was gradually added while grinding until a fairly good suspension was secured. The suspensions were then filtered through C. S. and S. no. 589 paper. Appropriate dilutions were made and three or four drops were placed on Bordet-Gengou media in Petri dishes. These small amounts of the suspension were spread over the surfaces of the media by means of a glass rod.

Following incubation for 8 weeks, colonies were transplanted from the Petri dishes to slants of egg media.

Colonies were developed from both the nonirradiated control and the irradiated cultures in twelve Petri dishes for each. However the irradiated culture had been transplanted, as well as the control, for two successive times to synthetic media without further irradiation in order to insure that only nonirradiated descendants of the irradiated cultures produced colonies.

The irradiated cultures had been X-rayed for a total of 847 hours (1,585,584 r units).

Types of Colonies Secured

No differences were noted in the relative numbers of R, S and I colonies secured from the descendants of the irradiated and nonirradiated cultures. This is of interest because the R type has been reported to be associated with attenuation of virulence and the S type with virulence. The irradiation cultures in this work have been associated with diminished virulence as compared with the virulence of the nonirradiated control cultures.

Tests for Virulence

Eight control and twelve irradiation strains were tested. Transplants of these were made from the egg slants to synthetic media. After three

weeks, masses of the growths from the synthetic media were pressed between absorbent papers to remove excess moisture, weighed and suspended in saline solution to give 2 mg. of bacilli per cc. of suspension.

TABLE 8

Nonirradiation colony strains

COLONY STRAIN INDEX	2 MG. BACILLI SUBCUTANEOUSLY					
	Animal number	Survival days	Macroscopical Tuberculosis			
			Right inguinal node	Spleen	Liver	Lungs
QC #7	1	50	++	+++	+++	++
QC #1	2	55	+++	++++	++++	++
QC #3	3	56	+++	++++	+++	++
QC #5	4	57	+++	++++	++++	++
QC #9	5	59	+++	++++	++++	+++
QC #2	6	60	+++	++++	++++	++
QC #6	7	85	++	++++	++++	+++
QC #4	8	109	+++	++++	++++	++
		$M_c = 66.3$				

Irradiation colony strains—Parent cultures X-rayed 847 hours (1,585,584 r units)

COLONY STRAIN INDEX	2 MG. BACILLI SUBCUTANEOUSLY					
	Animal number	Survival days	Macroscopical Tuberculosis			
			Right inguinal node	Spleen	Liver	Lungs
QXR #14	9	75	+++	++++	+	?
QXR #3	10	78	++++	++++	−	−
QXR #15	11	79	?	++++	++	?
QXR #4	12	149	+	++	++	−
QXR #17	13	179	++	++++	++	?
QXR #9	14	206	+	+	+	−
QXR #13	15	360	++	++++	++++	?
QXR #6	16	389	+	++++	+++	−
QXR #8	17	470	+	?	−	−
QXR #10	18	566[k]	−	−	−	−
QXR #5	19	578[k]	−	?	−	−
QXR #7	20	596	−	++++	+++	−
QXR #12	21	596[k]	−	−	−	−
		$M_{xr} = 332.3$				

[k] = killed

One guinea pig was used for each strain. The infecting dose was 2 mg. of bacilli injected subcutaneously in the right groin.

The results are recorded in table 8.

All of the eight subculture colony strains of table 8 from the non-irradiation parent culture may be considered as virulent.

Of the thirteen subculture colony strains from the irradiation parent culture recorded in table 8, three were virulent, three were moderately

TABLE 9

COLONY STRAIN INDEX	2 MG. BACILLI SUBCUTANEOUSLY					
	Animal number	Survival days	Macroscopical tuberculosis			
			Right inguinal node	Spleen	Liver	Lungs
Q X-ray #9	1	320		++++	++++	−
	2	345		++++	++++	++
	3	444		++++	++++	++++
	4	452°				
		M = 390.3				
Q X-ray #12	5	412[k]	−	−	−	−
	6	272[x]	?	?	−	−
	7	271[x]	−	−	−	−
	8	257[x]	−	++	−	−
	9	34[x]	+	−	−	−
	10	198[p]	−	−	−	−
		M = 240.6				
Q Control #7	11	60		++++	++++	+++
	12	68		++++	++++	+++
	13	128		++++	++++	++++
		M = 85.3				
Parent Control Culture	14	72	+++	++++	++++	++
	15	103	+++	++++	++++	+++
	16	39	++++	++++	++++	+++
		M = 71.3				

° = alive but in poor condition
[x] = cause of death not determined
[p] = paralyzed
[k] = killed

attenuated and seven were considerably attenuated. The three killed animals were in good condition and only one of these had probable macroscopical tuberculosis of the spleen.

Two of the subculture colony strains from the irradiation group and

one from the nonirradiation control group listed in table 8 were tested on groups of four guinea pigs.

The parent nonirradiation culture was also tested. The infecting dose was 2 mg. injected subcutaneously.

The results are recorded in table 9.

Attenuation of two of the subcultures of the irradiation culture was confirmed.

In the QXR no. 12 strain group, animal no. 8 was the only one with macroscopical evidence of tuberculosis of the spleen, histological examination of which demonstrated tubercles with fibrosis. Animal no. 10, besides being paralyzed, had an abscess in the right side of the neck, smears from which showed staphylococci, streptococci and diplococci and no acid-fast microörganisms.

In four animals the cause of death was not determined.

The subculture nonirradiation control strain and its parent culture were again shown to be virulent.

Colony Strain Experiment 2

In September, 1936, more colonies were planted. The irradiation was for a total of 1,092 hours (2,044,224 r units). Two serial transplants were made to fresh synthetic media without further irradiation. There had been no irradiation of the bacilli for over 6 weeks. The growth used as the source of colonies was 22 days old and the preparation of the suspensions of bacilli for the colonies before filtering was as described for colony experiment 1. Part of the suspension of bacilli in saline was not filtered through paper in order to duplicate the technique of Smithburn (16). Another part was filtered through paper as in colony strain experiment 1. Dilutions were made to provide well isolated colonies in order to facilitate removal of the latter for transplanting. Three or four drops were spread over the surfaces of Corper's and Cohn's egg media (17) adjusted to a pH 6.4 by the addition of 0.66 M Na_2HPO_4.

Types of Colonies Secured

Smithburn (16) stated that among human strains, including H37, the greatest number of smooth colonies occurred only at pH 6.4. No clean cut distinctions between the percentages of R, S and I colonies were observed in this investigation of the types of colonies from the attenuated irradiated and the virulent nonirradiated cultures. It was noted that the first colonies to develop were more of the type R, while

those developing late tended more to be of the S type. Observation of the colonies was discontinued at the end of two months.

Tests for Virulence

At the end of two months, 42 colonies from the filtered nonirradiated culture suspension and 42 from the filtered irradiation culture suspension were transplanted to slants of Corper's egg medium. These in turn were transplanted to synthetic media when needed for tests of virulence.

To shorten the time of the virulence tests it was decided to use the intracerebral method advocated by Smithburn (18) with the following changes adopted after a preliminary test: 0.1 mg. of bacilli in 0.03 cc. of suspension fluid and emulsification with sodium taurocholate. The smaller amount of injected fluid induced less trauma. The emulsification method of Corper and Cohn (19) was used to secure the most finely suspended bacilli possible to ensure more accurate dosages and more accurate tests.

The injections were made in the left side of the brain.

The large dose of 0.1 mg. was chosen in order to determine promptly whether or not avirulent or nearly avirulent strains were present.

All of the animals were allowed to die as it was soon determined that it was impossible to forecast death by as many as ten days, even if the animals appeared to be nearly dead.

Autopsies were done on all dead animals and smears made of the spleen and brain tissues to determine the presence or absence of bacteria, especially acid-fast microörganisms.

In general the reactions of the animals were as reported by Smithburn, although much longer ranges in the survival times of some of the groups occurred than in the groups of animals reported by him.

Only one animal was infected for each of the 84 strains reported below.

Similar suspension fluids with no bacilli and prepared exactly as those used to infect the brains of the animals were injected intracerebrally into four guinea pigs. The result showed that the method and technique were safe since the animals lived for 150 days and were in good health when killed.

The results are recorded in table 10 and in the graph based on the latter.

Fifteen of the animals infected with colony strains from the irradiated group of bacilli lived for an appreciable time longer than the longest lived of the controls.

TABLE 10

Intracerebral injections, 0.1 mg. bacilli

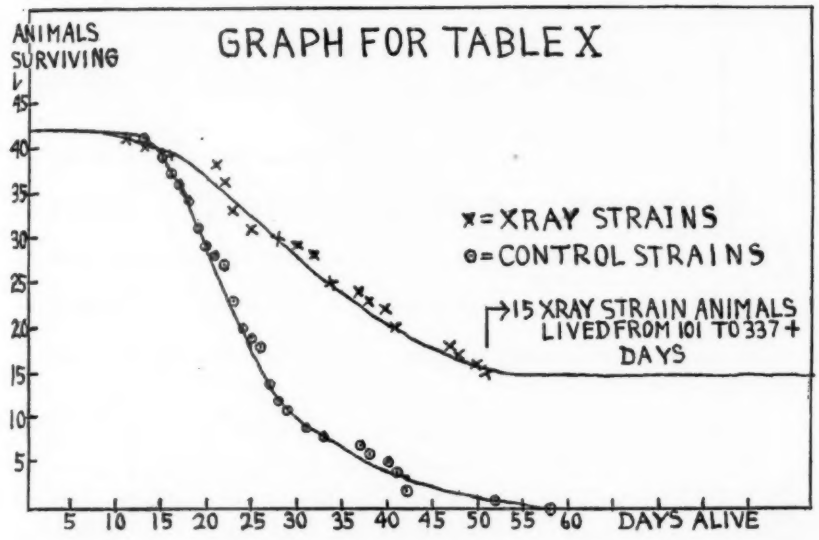
NONIRRADIATION			IRRADIATION—PARENT CULTURES IRRADIATED 1,092 HOURS (2,044,224 r UNITS)		
Survival days	Number of animals	Spleen smear, acid-fast micro-organisms	Survival days	Number of animals	Spleen smear, acid-fast micro-organisms
13	1	−	11	1	+
15	2	+?	13	1	+
16	2	+	16	1	+
17	1	+	21	1	+
18	2	+	22	2	+
19	3	+	23	3	+
20	2	+	25	2	+
21	1	+	28	1	+
22	1	+	30	1	+
23	4	+	32	1	+
24	3	+	34	3	+
25	1	+	37	1	+
26	1	+	38	1	+
27	4	+	40	1	+
28	2	+	41	2	+
29	1	+	47	2	+
31	2	+	48	1	−
33	1	+	50	1	+
37	1	+	51	1	+
38	1	+	101	1	+
40	1	+	108	1	+
41	1	+	126	1	−
42	2	+	131	1	−
52	1	+	145	1	−
58	1	+	147	1	+
			150	1	−
			157	1	−
			182	1	−
			215	1	+
			222	1	+
			304	1	+
			337—3 still alive, 2 in good condition; 12/22/37		
M_e = 26.6 days			M_{xr} of short life group = 31.7 days M_{xr} of long life group = 199.9 days M_{xr} of entire X-ray group = 91.7 days		

The graph for table 10 shows a marked difference between the survival curves of the control and irradiation groups. On it is also indicated for the animals infected with the subculture colony strains descended from the irradiated parent cultures, the group of long survivals separate and distinct from the shorter lived group.

Smears from all of the spleens of the controls with one exception were positive for acid-fast microörganisms. Of the irradiation group, only one was negative for the shorter survivals and six were negative for the longer survivals.

As stated before, this was the result of an attempt to detect avirulent strains if present. If we take the previous colony strain experiment 1, table 8 and table 9, as a fair test of attenuation, it seems probable that a larger number of attenuated strains could have been detected if smaller numbers of bacilli had been injected in this last experiment.

Several of the animals in the irradiation group, after becoming slightly to moderately paralyzed in the left hind leg, recovered from the paralysis



at least temporarily and improved in health. This was not true for any of the controls after paralysis had developed.

Also noteworthy is the longer duration of life in many of the irradiation group after paralysis had set in. Not all of the animals in either group developed paralysis. The average length of life after paralysis started in the X-ray group was 30.1 days and in the control group it was 5.7 days.

Colony Strain Experiment 3

Two of the nonirradiation colony strains and two of the irradiation colony strains of colony strain experiment 2, table 10, where the animals had survived for brief periods, were again tested on a larger number of animals. Subcutaneous injections in addition to the intra-

TABLE 11

Same colony subcultures recorded in table 10. Parent X-ray cultures irradiated 1,092 hours (2,044,224 r units)

		INTRACEREBRAL 0.1 MG. BACILLI				SUBCUTANEOUS 2.0 MG. BACILLI					
								Macroscopical Tuberculosis			
Colony strain index	Previous survival days	Animal number	Survival days	Paralysis	Spleen smear, acid-fast bacilli	Animal number	Survival days	Right inguinal node	Spleen	Liver	Lungs
Control no. 21	15	1	26	++++	+	5	91	++	++++	++++	++++
		2	13	−	+	6	47	++	++++	++++	−
		3	27	++++	+	7	66	++++	++++	+++	+++
		4	22	++	+	8	70	+++	++++	++++	+++
			M = 22				M = 68.5				
Control no. 6	22	9	17	++	+	13	62	++++	++++	++++	+++
		10	14	−	+	14	46	+	++++	++++	−
		11	20	+++	+	15	79	+++	++++	++++	+++
		12	25	++	+	16	70	+++	++++	++++	+++
			M = 19				M = 64.2				
Control no. 22	58	17	18	++	+	21	36	++++	++++	++++	++
		18	23	++++	+	22	46	++++	++++	++++	++
		19	33	++	+	23	56	+++	++++	++++	+
		20	17	++++	+	24	69	++	++++	++++	−
			M = 22.7				M = 51.7				
Control no. 18	52	25	23	+	+	29	95	+++	++++	++++	+++
		26	18	−	+	30	117	−	++++	++++	++++
		27	49	++++	+	31	64	+	++++	++++	+++
		28	25	++	+	32	67	+++	++++	+++	+
			M = 28.7				M = 85.7				

X-ray no. 36	13	33	52	+++	+	37	269[k]	+?	++++	+++	−
		34	20	−	−	38	139	−	+++	+++	++++
		35	19	−	+	39	269[k]	+	++++	++++	−
		36	38	++	+	40	89	+	++++	++++	−
			M = 32.2				M = 191.5				
X-ray no. 38	16	41	6[x]	−	?	45	267[k]	++	++	−	−
		42	25	−	+	46	267[k]	++	++	++	−?
		43	85	+++	−	47	89	?	++++	++++	−
		44	34	++++	+	48	267[k]	+++	++++	++++	+++
			M = 48				M = 222.5				
X-ray no. 7	145	49	28	+++	+	53	147	++	++++	+++	−
		50	37	+	+	54	254[k]	+?	++++	+++	−
		51	76	++++	+	55	254[k]	++++	++	++	−
		52	13′	−	+	56	86	++	++++	−	−
			M = 38.5				M = 185.2				
X-ray no. 3	182	57	69	++++	+	61	166	−	+++	++	−
		58	18	++	+	62	255[k]	?	+?	−	−
		59	22	++++	+	63	53	+++	++++	++	?
		60	27	−	+	64	255[k]	?	++	++	−
			M = 34				M = 182.3				

[x] = cause of death unknown; not counted
′ = pneumonia
[k] = killed

cerebral injections were made on groups of four animals for each of the strains.

The same was done for two long-survival strains from the irradiation subcultures and for the two longest-survival strains from the control subcultures of the same group.

The subcutaneous doses were 2 mg. of bacilli in 0.6 cc. of saline and the intracerebral doses were 0.1 mg. in 0.03 cc. The emulsification of the bacteria by sodium taurocholate was again done. All of the infecting doses of bacilli from any particular strain were taken from the same suspension.

The results are recorded in table 11.

The descendants of these colonies from the irradiated cultures were again shown to be attenuated as compared with the colony subcultures of the control cultures. This was true for both the intracerebral and subcutaneous injections. The same kind of statistical inquiry as for group 2, table 2, supports this.

Intracerebral injections: Control no. 22 colony strain, which on the single preliminary test had a survival time of 58 days, now had for its longest survival time 33 days and an average survival time of 22.7 days. Control no. 18 strain had for its longest survival time 49 days which approximates its single preliminary test of 52 days and had for its average survival time 28.7 days. It is to be concluded, then, that the controls are to be classed as virulent, especially when we consider the survival times for the subcutaneous injections for the four control colony strains with their averages of 68.5, 64.2, 51.7 and 85.7 days for groups of four animals each.

The X-ray strains were shown to be attenuated as compared with the controls. The X-ray no. 36 and no. 38 strains with their preliminary survival times of 13 and 16 days respectively had averages of 32.2 and 48 days. The X-ray strains no. 7 and no. 3, compared with the preliminary tests, had shorter survival times, but had average survival times greater than those of the controls.

Subcutaneous injections: The X-ray strains were shown to be definitely attenuated, nine out of sixteen animals infected being killed at the end of 254 to 269 days. All of the animals infected with the X-ray strains had tuberculosis when autopsied. It is notable that one out of four animals in each group infected with the X-ray strains died rather promptly and this indicates a probable greater susceptibility to tuberculosis of these particular animals.

TABLE 12

Strains from X-rayed cultures. Parent cultures irradiated 1,092 hours (2,044,224 r units)

COLONY STRAIN INDEX	INTRACEREBRAL INJECTIONS 0.1 MG. BACILLI			
	Previous survival days	Animal number	Survival days	Paralysis
X-ray no. 6	324°	1	52	+
		2	12 hours‡	
		3	49	+
		4	28	?
			M = 43	
X-ray no. 31	337°	5	73	?
		6	183°	+
		7	73	+
		8	61	+
			M = 97.5	
X-ray no. 21	304	9	118	+
		10	50	+
		11	181°	−
		12	61	−
			M = 102.5	
X-ray no. 40	215	13	87	−
		14	61	+
		15	28	−
		16	180ᵏ	−
			M = 89	
Q X-ray no. 7	§	17	75	+
		18	54	+
		19	12 hours‡	
		20	26	−
			M = 51.6	
X-ray no. 33	336°	21	37	+
		22	93	+
		23	142	+
		24	123	+
			M = 98.7	

‡ = animal died in 12 hours and eliminated from further consideration
ᵏ = killed
° = animal alive
§ = not tested by intracerebral route; subcutaneous injection of 2 mg. resulted in death from tuberculosis on 596th day

Colony strains X-ray no. 7 and X-ray no. 3 of table 11 were chosen because the preliminary single test animals of colony experiment 2 and table 10 had then survived for 119 and 116 days respectively and were in good health.

Five other irradiation strains were next tested again for virulence because their preliminary test animals of colony experiment 2 and table 10 had lived for longer times and were in good health. In addition, one other irradiation colony strain, QXR no. 7, of colony experiment 1, table 8, was tested.

The intracerebral method of infection was employed, the doses and technique being the same as before.

The results are recorded in table 12.

The survival times of these groups again were longer than for the controls (table 11). Two animals died within 12 hours after the injections and were eliminated from further consideration. Three animals, of whom one is dying and one was killed when in good condition, survived 180 days. Three of the preliminary test animals are alive 337 days and two of these are in good health.

Q X-ray no. 7 strain, of colony experiment 1, table 8, which previously had associated with it the long survival time of 596 days following a subcutaneous injection of 2 mg., had an average of 51.6 days following intracerebral injections of 0.1 mg. bacilli.

DISCUSSION

The subcutaneous method of infecting the animals has demonstrated definitely an attenuation of virulence in the irradiated cultures. The intracerebral method has indicated the same, but smaller doses of bacilli would probably have made this more certain.

Large doses of bacilli from colony subcultures were injected into the brains in order to determine promptly the probably avirulent strains. The tissue reactions may have been so great even with attenuated bacilli that paralysis and death resulted because of pressure and not because of the toxic properties of the bacilli. But even with the large doses used, 15 out of 42 irradiation strains in the preliminary tests were associated with much longer survival times than were any of the controls. The preliminary test animals for three of these X-ray strains are now living 337 days.

There have been wider ranges of survival times noted in some of

these brain groups than were reported by Smithburn. This can probably be accounted for on the basis of attenuation of the particular colony strain cultures tested and the very large infecting doses used.

Irradiation with X-rays did not alter the hydrogen ion concentration and growth promoting properties of the synthetic media. Any fluorescence or phosphorescence resulting from the X-rays did not inhibit the growth of the bacilli.

It seems reasonable to suppose that the X-rays directly influenced the tubercle bacilli in such a way that their descendants had their virulence considerably attenuated. However, either the media may have been altered by the X-rays in such a way that attenuation resulted, or some unexplainable spontaneous attenuation may have occurred. No effort has been made to account for the first hypothesis. As against the second hypothesis may be cited two facts: (*1*) that increasing attenuation occurred with increasing amounts of irradiation and (*2*) the controls were always treated in exactly the same way as were the irradiated except for the irradiation by X-rays.

CONCLUSIONS

Evidence has been presented that irradiation of successive cultures of virulent human tubercle bacilli with X-rays over a long period of time has resulted in the virulence being considerably attenuated. The attenuated irradiated parent cultures were shown to still contain a small percentage of nonattenuated virulent bacilli, as shown by tests of colony subculture strains.

No increase of virulence in any of the subcultured colony strains was demonstrated as a result of irradiation with X-rays.

Complete loss of virulence has not been demonstrated.

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THE BROMSULPHALEIN TEST AND BLOOD CHOLESTEROL IN PULMONARY TUBERCULOSIS[1]

S. A. LEVINSON AND H. A. SIEGAL

Bacmeister and Henes (1), among others, have shown that a low blood cholesterol exists in acute stages of syphilis, leprosy and tuberculosis. They found normal cholesterol values in early tuberculosis, but there was an appreciable reduction in the far advanced cases associated with cachexia. The explanation for the hypocholesterolaemia, as set forth by Eichelberger and McClusky (2), is that a definite disturbance in the cholesterol metabolism exists in tuberculosis, which is based upon the demand of the tissues for the immunizing properties of cholesterol against infection. These observers also reported that the disturbance of the cholesterol in the tissues affects the water content, since it had been shown that tissues with increased cholesterol have the greatest power of imbibing and holding water. On this basis they explain the great emaciation and dehydration of body tissues, found in far advanced tuberculosis with a low cholesterolaemia. A rising or stationary hypercholesterolaemia indicates resistance and immunity, while hypocholesterolaemia represents a diminution of these factors against tuberculosis (2).

Some observers, particularly von Babarczy (3), showed that hypocholesterolaemia occurs in cases with increased sensitivity to tuberculin. Levinson (4) observed an increase in the cholesterol level of the blood on feeding animals egg yolk and cholesterol in oil, but did not produce an appreciable alteration of their resistance or protection against infection by the tubercle bacillus. King and Bruger (5), in a series of studies of tuberculosis with amyloid nephrosis and oedema, showed that 45 per cent of the cases terminated fatally within six months, despite a high blood cholesterol.

In an attempt to determine the mechanism of the production of hypocholesterolaemia, Leites (6), Muller (7), and others studied the relationship of the reticuloendothelial system to cholesterol metabolism.

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They produced experimentally a definite decrease in plasma cholesterol following the intravenous injections of various colloidal substances, such as collargol, colloidal iron and olive oil emulsions, resulting in an increase or stimulation of the functional activity of the reticuloendothelial system. Leites (6) produced a "block" of the reticuloendothelial system with colloidal silver and, after administering olive oil, found a retardation of the normal fall of cholesterol in the blood. He explains this as due to a decrease in the functional activity of the reticuloendothelial system. Similar observations have been noted clinically in cases of haemolytic anaemia, with its increased blood destruction and bile pigment formation. This condition is manifested by a low blood cholesterol, apparently due to a stimulating action of the reticuloendothelial system. With a decrease in the functional activity of this system, as obtained during remissions in pernicious anaemia, the blood destruction and bilirubinaemia decrease and the cholesterol level rises. It appears, then, that in those conditions in which there is some alteration in the functional activity of the reticuloendothelial system there is an accompanying effect on the metabolism of cholesterol.

Schellong and Eisler (8), Klein and Levinson (9), and others have shown that the halogenated pthaleins are removed from the blood by the reticuloendothelial system. Bromsulphalein represents this latter group of dyes, and it was therefore chosen, essentially as an index of the state of functional activity of the reticuloendothelial system.

Cantarow and McCool (10), in the course of their studies on hepatic function in various terminal states, observed a significant decrease in the plasma cholesterol in cases that showed bromsulphalein retention (decrease of 8.5 to 41.3 per cent). However, they also observed a decline in the cholesterol level in cases with no bromsulphalein retention (8 to 30 per cent), apparently due to an alteration in the functional activity of the reticuloendothelial system resulting from the administration of the dye.

MATERIAL STUDIED

In the series of patients studied, 19 women and 9 men were selected who represented moderate to far advanced types of tuberculosis. Blood was drawn on fasting for the determination of cholesterol and icterus index, and immediately, while the needle was *in situ*, 2.0 mg. per kilogram body weight of bromsulphalein (11) were administered. Blood was drawn again after 5 and 30 minutes. No untoward reactions from

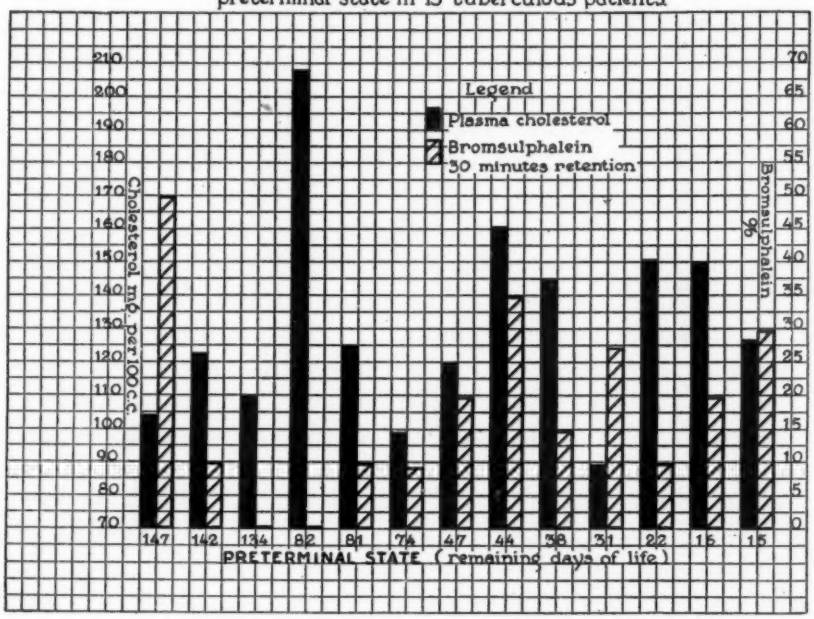
TABLE I

Comparative values of bromsulphalein dye retention and plasma cholesterol in 28 tuberculous patients

BROMSULPHALEIN 30-MINUTE READING	CHOLESTEROL	LIVING OR DEAD	AVERAGE CHOLESTEROL	AVERAGE MORTALITY
per cent	*mg./100 cc.*		*mg./100 cc.*	*per cent*
0	208	D		
0	202	L		
0	192	L		
0	174	L		
0	132	L		
0	110	D	169	33.3
5	180	L		
5	156	L		
5	153	L		
5	151	L		
5	135	L		
5	119	L		
5	112	L		
5	109	L		
5	104	L	135	0
6	125	L	125	0
8	104	D	104	100
10	151	D		
10	125	D		
10	123	D	133	100
15	145	D	145	100
20	150	D		
20	132	L		
20	120	D	134	66.7
30	127	D		
30	89	D	108	100
35	161	D	161	100
50	104	D	104	100
Total average 11.0	139.0	D:46%		

bromsulphalein were noted. All readings of bromsulphalein retention were made within 30 minutes following withdrawal of the 30-minute specimen. It will be noted that no cholesterol determinations were made following the administration of the dye. This was done in order to obviate the possible effect of the dye itself on the functional activity of the reticuloendothelial system. Cholesterol determinations were made according to the method of Bloor (12) and icterus index by means of the Meulengracht method (13).

Table II. Relationship of plasma cholesterol and the bromsulphalein liver function test to the preterminal state in 13 tuberculous patients



It will be observed (table I) that the mortality in the series of cases was high (46 per cent) and that the duration of life ranged from 15 to 148 days, with an average of 67.3 days from the date of the determinations.

Table II indicates the relationship of plasma cholesterol and the bromsulphalein retention to the preterminal state. The cholesterol readings of the patients who eventually died ranged from 89 to 208, with an average of 130.2 mg. per 100 cc. The average 30-minute bromsulphalein reading on these same patients was 18.7 per cent and ranged

from 0 to 50 per cent. Although 5-minute readings were also taken, they are not represented in tables I and II, but are recorded along with the more complete data in table III. No gradual decline in the cholesterol level is demonstrable as compared to the remaining days of life (table II), yet a definite hypocholesterolaemia exists, and in only 3 patients did the cholesterol level exceed 150 mg. per 100 cc. One patient (D. S.) showed a hypercholesterolaemia (208) and no 30 minute bromsulphalein retention. He had numerous cold abscesses, generalized tuberculous adenitis, tuberculosis of the spine and hip, tuberculous peritonitis, and generalized amyloidosis. This latter condition may explain the elevation of blood cholesterol. Of the 7 patients who died within fifty days following the determinations, all showed a definite 30-minute dye retention (10 to 35 per cent), and all but one (E. D.) a definite hypocholesterolaemia. It is interesting to note that, of the patients who died, none exhibited normal cholesterol and bromsulphalein readings at the same time.

The tests were repeated on three patients (L. B., D. S. and A.L.). There was little appreciable difference in the cholesterol readings of these patients; the two patients who died (L. B. and D. S.) showed a fixed low and high blood cholesterol respectively (104 to 106 and 208). Both these patients had a far advanced exudative pulmonary tuberculosis, one (L. B.) complicated by a right hydrothorax and tuberculous peritonitis with ascites; the other patient (D. S.) probably had amyloidosis. The other patient (A. L.), classified as far advanced B with tuberculous laryngitis, showed very little improvement, and revealed a tendency to a decrease in the blood cholesterol (151 to 145). This patient was transferred to the Municipal Sanitarium and could not be studied any further.

Table I indicates the comparative values of bromsulphalein dye retention and plasma cholesterol in all the tuberculous patients examined. The average cholesterol reading of all the patients was 139.0 mg. per 100 cc.; 145.0 mg. per 100 cc. the average of those remaining alive, as compared to 130 mg. per 100 cc. which was the average cholesterol reading of the patients who died. This table indicates more clearly the tendency to a decline in the cholesterol level as bromsulphalein retention increases. It also indicates the extreme gravity of the cases showing a marked retention and hypocholesterolaemia occurring simultaneously. Of the 12 patients who had a bromsulphalein retention of 10 per cent or more (30-minute reading), combined with a definite hypo-

TABLE III

Composite data of analysis on twenty-eight tuberculous patients

DATE	PATIENT	AGE	SEX	WEIGHT	DURATION OF ILLNESS	AVERAGE TEMPERATURE	SPUTUM	PALPABLE LIVER	ICTERUS INDEX	WASSERMANN	MENSES	BLOOD CHOLESTEROL	BROMSULPHALEIN LIVER FUNCTION PER CENT RETENTION		DIAGNOSIS	COURSE
													5 min.	30 min.		
				pounds		*degrees Fahrenheit*						*mg./100 cc.*				
2/21/36									5.0		Absent	104	100	50	FA-C—Rt. hydrothorax, peritonitis with ascites	Downhill
5/ 1/36	L. B.	34	F	90	11 mo.	99.4	Neg.	3 Fingers	4.0	Neg.	11 mo.	106	40	30		Died, 7/18/36
2/ 1/36	V. J.	25	F	86	2 mo.	98	Pos.	No	5.0	Neg.	Irreg.	132	0	0	MA-B—Tuberculous adenitis, laryngitis, basal consolidation	Absconded on pass 3/16/36
2/14/36	O. B.	26	F	80½	4 mo.	98.6	Pos.	No	7.0	Neg.	Irreg.	109	10	5	Bilat. FA-B—Cavitation, laryngitis, pneumothorax	Trans. to M.T.S.
2/14/36	A. B. (1st)	20	F	94	2 mo.	99	Pos.	No	6.0	Neg.	Reg.	125	8	6	MA-B—Infiltration, apical involvement	Trans. to M.T.S.
2/28/36	A. B. (2nd)	21	F	85	1 yr.	100	Pos.	No	7.0	Neg.	Irreg.	89	50	30	Bilat. MA-B—Tuberculous adenitis neck and axilla	Died 3/31/36
2/28/36	C. F.	52	F	129	6 mo.	99.4	Pos.	No	7.0	Neg.	Irreg.	119	10	5	MA-B—Pulmonary haemorrhage pneumothorax	Disch. 3/7/36 Cond. improved
3/13/36	N. H.	16	F	95	6 mo.	101.4	Pos.	No	7.0	Neg.	Irreg.	145	45	15	FA-C—Bilat. cavitation	Died 4/20/36
3/13/36									10.0		Meno-	151	10	5	FA-C—Bilat. cavitation,	Trans. to M.T.S.
5/ 1/36	A. L.	53	F	117	3 yr.	99	Pos.	1 Finger	10.0	Neg.	pause, 5 yr.	145	5	0	hoarseness, fibrosis	Cond. improving
3/27/36	S. D.	22	F	131	5 mo.	100.2	Pos.	No	8.0	Neg.	Irreg.	123	35	10	Bilat. FA-B—Cavitation, laryngitis, enteritis	Died 8/16/36

3/27/36	E. T.	29	F	88	13 mo.	100.4	Pos.	No	10.0	Neg.	Irreg.	127	60	30	Bilat. FA-B—Thick pleura, laryngitis	L. sup. laryngeal nerve resection; died 4/6/36
4/ 3/36	T. S.	33	F	83	6 mo.	100.6	Pos.	No	7.0	Neg.	Absent 6 mo.	104	35	5	Bilat.FA-B—Cavitation	R.H.D. 5/12/36
4/ 3/36	J. C.	44	F	68	3 mo.	99	Pos.	No	8.0	Neg.	Reg.	153	40	5	Bilat. FA-B—Infiltration	Absconded on pass 8/3/36
4/17/36	E. F.	33	F	151	Old case, thoraco-plasty 1932	98.6	Pos.	No	5.0	Neg.	Reg.	202	0	0	Old thoracoplasty, early infiltration, rt. upper, MA-B	Disch. 5/28/36 Improved
4/17/36	E. H.	18	F	108	4 mo.	100.2	Pos.	No	5.0	Neg.	Irreg.	112	30	5	Bilat. FA-C—Cavitation, rheumatic heart	Downhill Disch. 7/31/36
4/24/36	M. T.	29	F	94	1 yr.	100.6	Pos.	No	4.0	Neg.	Irreg.	104	15	8	Bilat. FA-C—Cavitation, laryngitis	Died 7/7/36
4/24/36	E. A.	52	F	86	2½ mo.	99	Neg.	1 Finger	5.0	Neg.	Meno-pause	159	30	15	Hypertensive heart disease with decompensation, hydrothorax	Disch. 6/26/36
5/ 8/36	A. M. (1st)	26	F	101	10 mo.	101	Pos.	No	6.0	Neg.	Irreg.	125	40	10	FA-B—Pott's disease, old thoracoplasty	Died 7/28/36
5/ 8/36	M. C.	35	F	104	8 yr.	99.4	Pos.	No	5.0	Neg.	Reg.	156	30	5	MA-B—Pneumothorax, left (50 per cent collapse)	Cond. good Disch. 6/24/36
5/15/36	A. G.	28	F	90	4 yr.	101	Neg.	No	5.0	Pos. Kahn Wass.	Irreg.	120	30	20	FA-B—Cervical adenitis, tuberculous peritonitis, syphilis with keratitis	Died 7/1/36

MTS = Municipal Tuberculosis Sanitarium.
RHD = Released to Health Department.
MA = Moderately Advanced.
FA = Far Advanced.
A, B, C } Severity of symptoms.

TABLE III—*Concluded*

DATE	PATIENT	AGE	SEX	WEIGHT	DURATION OF ILLNESS	AVERAGE TEMPERATURE	SPUTUM	PALPABLE LIVER	ICTERUS INDEX	WASSERMANN	MENSES	BLOOD CHOLESTEROL	BROMSULPHALEIN LIVER FUNCTION PER CENT RETENTION		DIAGNOSIS	COURSE
													5 min.	30 min.		
				pounds												
5/15/36	A. M. (2nd)	38	F	78	15 mo.	99.4	Pos.	No	4.0	Neg.	Irreg.	110	35	0	MA-B—Pneumothorax	Died 9/26/36
5/21/36									7.0			208	15	0	MA-B—Amyloidosis, tuberculous adenitis, spine, hip, cold abscesses	Died 8/11/36
6/18/36	D. S.	29	M	102	6 mo.	100.4	Neg.	No	7.0	Neg.		208	40	30		
5/21/36	R. E.	19	M	89	1 yr.	100	Neg.	No	5.0	Neg.		132	35	20	MA-B—Tuberculosis of 6th rib	Trans. to M.T.S. 8/25/36
5/29/36	H. D.	29	M	138	6 mo.	99	Pos.	No	6.0	Neg.		174	30	0	MA-B—Pneumothorax	Improved Disch. 9/30/36
5/29/36	K. D.	36	M	118	1 yr.	99.6	Neg.	No	6.0	Neg.		150	45	20	Tuberculous lung abscess, pneumothorax	Died 6/14/36
6/18/36	W. K.	39	M	83½	3 mo.	99.2	Neg.	No	3.0	Neg.		192	0	0	FA-B—Infiltrative-pneumonic consolidation	Improved Disch. 7/28/36
6/18/36	N. F.	36	M	134	6 mo.	98.6	Neg.	3 Fingers	5.0	Neg.		197	80	0	Alcoholic cirrhosis with epistaxis	Trans. to Med. Ward
6/25/36	E. S.	35	M	119	6 mo.	101	Pos.	No	4.0	Neg.		151	30	10	Bilat. MA-B—Cavitation	Died 7/17/36
6/25/36	J. C.	45	M	156	4 yr.	99	Pos.	No	5.0	Neg.		135	100	5	Bilat. MA-B—Cavitation, old phrenicectomy	Disch. 7/23/36
7/ 2/36	A. L.	19	M	125	19 mo.	99.2	Neg.	No	5.0	Neg.		180	100	5	FA-B—Pneumothorax (70 per cent)	Cond. about same, still a patient
7/ 2/36	E. D.	16	M	110	3 mo.	100	Pos.	No	4.0	Neg.		161	100	35	FA-C—Cavitation	Died 8/15/36

cholesterolaemia, 11 (91 per cent) terminated fatally. Two patients (N. F. and E. A.) were found later to be nontuberculous and were transferred to the proper medical wards. They do not figure in any of the calculations made.

Table III represents a composite of the data pertinent to each case studied. The ages ranged from 16 to 53. The duration of illness was from two months to eight years. Icterus index values were taken as a check on liver function, to determine whether the cases showing bromsulphalein retention would also reveal a hypobilirubinaemia. It ranged from 3 to 10.0 on all patients, with an average of 5.9. The average among the patients who died was 5.0. The Wassermann test was positive in only one patient. This patient had a syphilitic interstitial keratitis.

Irregularities of menstrual function was a very characteristic finding in 16 of the 20 women examined, presenting either delayed or absent menses. Two patients, who had an amenorrhoea of six and eleven months, had a definite hypocholesterolaemia (104 in each case). Since recent studies have tended to establish cholesterol as the basic chemical component of the female sex hormone, the hypocholesterolaemia in these women with absent or delayed menses may play an important rôle in the deficient synthesis of this important hormone, assuming a regulatory action of this hormone on normal menstrual function.

CONCLUSIONS

1. The bromsulphalein liver function test and blood cholesterol were studied in 28 cases of far advanced pulmonary tuberculosis. These tests can be used as an index in the prognosis of the disease condition.

2. The combination of hypocholesterolaemia with bromsulphalein retention indicates extreme gravity.

3. The hypocholesterolaemia and bromsulphalein retention may be related to the functional activity of the reticuloendothelial system as evidenced by the greater demand for cholesterol by the organ. The degree of stimulation of the reticuloendothelial system can be measured by the amount of bromsulphalein dye retention. The greater the stimulation the more retention of the dye.

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THE LEVINSON TEST IN TUBERCULOUS MENINGITIS[1]

MORRIS GLEICH

Five years ago we made a study of the Levinson test (1). The present paper is a continuation of the work (May, 1932 to December, 1936). We feel that many physicians, unacquainted with this test, will benefit by its use in cases suspected of tuberculous meningitis.

Twenty years ago, Tashiro and Levinson (2) described the behavior of protein in meningitic spinal fluid in the presence of alkaloidal and metallic precipitants. They found that protein of epidemic cerebrospinal meningitic fluid reacted electro-positively when mixed with a solution of sulphosalicylic acid (alkaloid precipitant) and electronegatively when mixed with a bichloride of mercury solution (metallic precipitant). The H-ion concentration of the meningitic spinal fluid and the nature of the precipitants formed the basis for the Levinson test. They also found that the protein in tuberculous meningitic spinal fluid reacted electro-positively with bichloride of mercury solution and electro-negatively with sulphosalicylic acid solution.

If serum has been given to a patient, intrathecally, as for meningococcus meningitis, or if blood contaminates the spinal fluid, the Levinson test should not be done. Serum and blood added to spinal fluid render the latter alkaline. This alkalinity plays an important rôle in the test. Such spinal fluid gives a pseudopositive Levinson test.

The Levinson test is done as follows: One cc. of spinal fluid is placed in each of two test tubes, 8 mm. in diameter. To one is added 1 cc. of a 1 per cent solution of mercuric chloride and to the other, 1 cc. of a 3 per cent solution of sulphosalicylic acid. The tubes are shaken, stoppered and allowed to stand at room temperature for twenty-four to forty-eight hours. At the end of this time the column of precipitate in each test tube is measured in millimetres. When the height of the precipitate in the first test tube is at least twice that of the precipitate in the second test tube, the test is positive.

There were thirty cases of tuberculous meningitis, each with a positive Levinson test. In twenty-three of these cases tubercle bacilli were found

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in the spinal fluid. In six cases tuberculosis was noted at autopsy. One case revealed tuberculosis at autopsy and also showed tubercle bacilli in the spinal fluid.

Thirteen cases of nontuberculous meningitis had a negative Levinson test. These included ten cases of meningococcus meningitis and three patients suffering from poliomyelitis.

There were eight patients with a positive Levinson test and no tuberculous meningitis. One had an intracranial haemorrhage with multiple lacerations; two had cerebral haemorrhage with hypertensive heart disease; one was diagnosed as encephalitis lethargica; three were epileptics; one had a staphylococcic meningitis; another, subarachnoid haemorrhage with right hemiplegia. All of these cases showed a positive Levinson test because their spinal fluid contained blood or serum had previously been given intraspinously.

CONCLUSION

Of 30 cases of tuberculous meningitis all gave a positive Levinson test. In 76.6 per cent of these patients tubercle bacilli were found in the spinal fluid. Twenty per cent of the cases showed tuberculosis at autopsy. In one case tuberculosis was noted at autopsy and tubercle bacilli were demonstrated in the spinal fluid.

None of 13 cases of nontuberculous meningitis had a positive Levinson test. One will occasionally find cases of nontuberculous meningitis or patients with other brain lesions who give a positive Levinson test. If we remember to refrain from performing a Levinson test on the spinal fluid which is contaminated by blood, or where serum has been previously given intrathecally, such pseudopositive Levinson tests will be avoided.

I am indebted to Dr. Solomon Weintraub, Director Pathology Laboratory, and to Dr. Thomas Patrick, former House Pediatrician, for their splendid coöperation. I wish also to acknowledge with thanks the technical assistance of Miss Roslyn Weintraub and Miss Elaine Phaire of the Pathology Laboratory.

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QUANTITATIVE METHOD FOR ESTIMATING THE NUMBER OF TUBERCLE BACILLI IN SPUTUM[1]

ELIZABETH F. JORDAN

The number of tubercle bacilli excreted in the sputum of a patient suffering from tuberculosis is a matter of more than academic interest. To the clinician who observes the course of the disease it may be a guide to therapy and a landmark in prognosis; to the public health nurse and the social service worker it is the chart from which they may plot the course which will least handicap the patient while protecting the family and the community.

As universally used, the Gaffky count (1), with the modification of terms proposed by Brown (2), is an attempt to provide needed information but the method of obtaining the count only approximates a quantitative method.

In laboratories where these counts are made routinely, it is not unusual to find duplicate slides, made from a single specimen, showing a wide variation in the number of acid-fast bacilli present. A superficial observation of the nature of sputum gives an adequate explanation of such results. When the specimen comes to the laboratory it is far from homogeneous, and the amount of material on the slide, the number of microscopical fields searched, and, to a minor degree, the size of the field, all play a part in determining the Gaffky count. For these reasons comparable counts are difficult to obtain, and the literature contains many warnings against the unguarded use of this procedure.

The Hughes technique (3) was designed to correct the inaccuracies of the Gaffky count and to furnish a method by which the number of acid-fast bacilli in a specimen of sputum could be determined by quantitative methods. Briefly, the test is as follows:

One cubic centimetre of a 10 per cent solution of sodium hydroxide is pipetted into a test tube or small bottle and 2 cc. of sputum and a few glass beads are added. The mixture is then agitated in a shaking machine for 30 minutes. The difficulty of measuring viscous sputum is

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overcome by the use of glass tubing calibrated to deliver the desired quantity. A syringe or a glass mouthpiece attached by rubber tubing facilitates drawing the sputum into the glass tubing. Digestion takes place during the shaking process. Smears are made from the resulting mixture, spreading evenly one loopful of the digest and one loopful of sterile serum on an area of approximately 400 sq. cm. (381 sq. cm. according to calculation). This area is marked on a one-inch wide microscope slide by drawing a line 15 mm. from one end with a diamond pencil. The smear is air dried, fixed with heat, and stained by the Ziehl-Neelsen method. The loop recommended is the standard 3 mm. loop with an exact inside diameter and a welded joint. Ten scattered fields are counted, and the average number of bacilli per field is calculated. Hughes states that the loop delivers 3.5 cmm. and the formula therefore for calculating the number of tubercle bacilli per cubic millimetre of sputum is: average number of bacilli per field $\times$ 1.5 (the dilution factor) $\times$ the number of microscopical fields in the smear divided by the volume of the specimen in cubic millimetres, in this instance 3.5. The number of microscopical fields in the area of the smear may be determined for any microscope by the use of a haemocytometer marked into squares measuring .05 mm.

The present study was originally undertaken for the purpose of reviewing the Hughes technique, since, if generally applicable, the method would give a more accurate determination of tubercle bacilli than the Gaffky count which is so widely used.

Selection of specimens: Hughes suggested, since his method is of value only when the sputum is positive and is more time-consuming than the ordinary method, that its use be limited to specimens already diagnosed as positive. It appears from the studies here reported that Hughes's method might be further limited to those specimens showing a Gaffky of V or more. The point is made clear by the data in table 1.

In table 1 the numbers of microörganisms in the specimens examined according to the Hughes technique are too small to be significant; the probable error being almost as great as the mean. This disparity between specimens examined by both methods is the rule rather than the exception. The amount of material used in making the slide can be varied only within narrow limits since the area used on the slide is relatively small.

The explanation of these data obviously lies in the nature of the sputum. When, as is so frequently the case, the tubercle bacilli are

not distributed evenly throughout the specimen a bit of purulent material may be used to make the Gaffky count. In the Hughes method there may be a few or only one such particle which in the process of digestion becomes evenly distributed throughout the mixture which is further diluted by the sodium hydroxide. The number of bacilli per microscopical field is thereby reduced, and the probable error increases as the number of observations decreases.

Method of sampling: In material which is difficult to handle because of its nature and is made up of elements which tend to separate upon

TABLE 1

Comparison of Gaffky and Hughes counts on the same specimens

SPECIMEN	DATE		ACID-FAST BACCILLI PER OIL IMMERSION FIELD										MEAN	P.E.*
			1	2	3	4	5	6	7	8	9	10		
1	11/16	Gaffky	8	14	0	16	9	9	3	15	8	4	8.6	3.4
1	11/16	Hughes	1	0	1	0	0	0	0	0	0	0	0.2	0.5
2	11/25	Gaffky	22	28	15	11	13	2	11	9	6	14	13.1	4.7
2	11/25	Hughes	2	0	2	1	1	0	0	5	1	2	1.4	0.9
3	1/5	Gaffky	5	9	3	4	6	17	13	7	4	10	7.8	2.8
3	1/5	Hughes	1	0	1	1	2	3	0	0	0	0	0.8	0.6

* P.E. = The probable error of the mean.

standing, the difficulties of sampling cannot be overemphasized. In many cases it is difficult to secure a preliminary mixing which will give a representative sample even when the volume of the sample is as large as 2 cc. In 24-hour specimens it is often impossible. Thus, slides made from each of two separate digests of the same material showed the following counts:

Number of acid-fast bacilli in ten fields

DATE	DIGEST	SLIDE NUMBER			
January 7	1	22	21	19	23
January 7	2	35	30	35	33

Such discrepancies between digests supposedly identical are frequent.

Use of the loop: Little has been written about the use of a platinum loop in volumetric work although Asheshov (4) used this method in the dilution of bacteriophage. In the Hughes study a platinum loop

3 mm. in diameter with a wire 0.4 mm. in thickness is stated to deliver approximately 3.5 cmm. Since such an amount is difficult to measure directly, weighings were used to check the accuracy of the procedure. Many groups of weighings were made in an effort to determine the weight of a digest before and after a loopful was removed. The weighings confirmed what had previously been suspected—that in the hands of a single individual it is possible to remove loopfuls which vary less than 10 per cent from each other. If, however, the loop is withdrawn in the usual fashion with the plane of the loop parallel to the surface of the liquid, the weight of the material withdrawn may vary from 2 to 16 mg. The former weight represents, of course, a thin film of liquid, the latter is spheroidal. In our hands a loopful withdrawn parallel to the surface weighed about 13 mg.; with the loop withdrawn at right angles the weight was about 10 mg. It is realized that the weights given here are not the exact equivalent of the volume in cubic millimetres, but weighings seemed to be a feasible method of testing the "loopful" as a volumetric instrument.

In this connection it should be remembered that sputum, even after digestion, varies greatly in viscosity and that the more viscous it is the larger the "loopful" tends to be. The use of pipettes graduated to hundreths of a cc. has been tried and would seem to be a more accurate means of measuring such small quantities. Their use does not add appreciably to the time required for making slides.

The distribution of microörganisms on a slide is frequently uneven, particularly so when the fluid does not dry rapidly. No mention is made by Hughes of the method used to secure an even mixing of the serum and digested sputum, but his figures show that this was accomplished. A perfect mixture with even distribution of microörganisms presented difficulties never entirely overcome by us.

DISCUSSION OF HUGHES TECHNIQUE

The Hughes technique is a step toward greater accuracy in determining the number of tubercle bacilli in sputum. The fundamental difficulties of the method are of such a character that its use may lead to fallacious assumptions, unless the results are interpreted with caution.

The significance of the results obtained rests upon an assumption which may or may not have basis in fact, namely, that the volume of sputum in a given case bears a constant ratio to the number of organisms. Does a fall in the number of bacilli per cc. in the sputum of a case which

was examined at frequent intervals by Hughes represent greater dilution of the sputum with saliva and does a rise mark the draining of another tubercle? Whatever may be the clinical significance, from the standpoint of public health, there is little difference between 300,000 bacilli per cc. when the total volume of sputum in a day is 10 cc. and 30,000 bacilli per cc. when the total volume is 100 cc.

In conclusion, it may be stated that the dilution of the specimen which restricts the use of this method to those patients which excrete enormous numbers of tubercle bacilli, the difficulty of obtaining a complete mixture of the serum and digest and the large amount of time involved in making the test would seem to make the Hughes method not practical.

PROPOSED METHOD

When preliminary tests of the Hughes method seemed to indicate that it was not adapted to the use of the Division of Infectious Diseases of the Department of Medicine of the New York Hospital and Cornell University Medical College, it was suggested that research directed toward the same end would be of value. The method outlined below, based in part upon the Hughes technique, has seemed to fulfill more nearly the requirements of a quantitative method. In addition, it should be applicable to all types of laboratory specimens and should give reasonably comparable results in the hands of different workers.

The specimen of sputum as received in the laboratory of the Division from the clinic or hospital usually is a 72-hour sample. It is contained in a large wide-mouthed bottle with straight sides. Four per cent sodium hydroxide, in a volume roughly equal to the volume of sputum, is added at once and the bottle then agitated in the shaking machine for thirty minutes. This mixture is then transferred to centrifuge tubes and spun at high speed for 30 minutes. The supernatant fluid is then drawn off and a loopful of the sediment is used to make a smear which is air-dried, fixed, stained in the usual manner with Ziehl-Neelsen and counterstained with brilliant green. Such concentrates were made available for this study after the Gaffky count had been made. Gaffky counts subsequently quoted were made on these specimens in the laboratory of the Division. The figures obtained by the new method about to be described will not represent the total number of microörganisms in the specimens, for when received these specimens had already been depleted by the loopful used for the routine Gaffky count. Since it is the method in which we were primarily interested rather than in

the results as such, this fact did not detract from their value. Because we were testing the accuracy of a method, many counts were made on the same concentrate in some cases on several days. The results for each day are considered as a unit.

On theoretical grounds it was thought more suitable to apply quantitative methods to the sediments resulting from concentrations than to raw sputum. Not only was the sediment much more homogeneous in character and therefore not subject to gross errors in sampling but the bacilli were concentrated, making an estimation possible in all positive sputa except perhaps those which were Gaffky I. Furthermore, there would seem to be many advantages in assigning to a specimen of sputum a number which would represent the per diem excretion of tubercle bacilli in sputum.

Procedure: The sediment from the centrifuge tube in which the mixture of sputum and 4 per cent sodium hydroxide had been spun for 30 minutes at high speed is washed with sodium chloride solution into a small test tube, which has a volume of 1.5 cc. indicated by a file mark. The centrifuge tube is twice rinsed with a small amount of salt solution and the rinsings added to the sample. The volume of the combined sediment and rinsings is then made up to 1.5 cc. by the addition of saline solution. Three or four glass beads are added to the tube which is then stoppered and agitated in the shaking machine for 30 minutes. (Others in the laboratory have found that a hard shaking by hand for 5 minutes is equally satisfactory.) The slides are marked, as Hughes suggests, with a diamond pencil line drawn 15 mm. from one end across a slide 1 inch wide. After cleaning with acid alcohol, a loopful of sterile serum is spread over the area marked off. The serum dries almost immediately and serves as a fixative. A measured amount of the digested concentrate is added using a pipette graduated in hundredths of a cc. This is spread as evenly as possible over the layer of serum. For the first count, four slides are made from each specimen with .02, .04, .06 and 0.1 cc. respectively. This is in order to obtain a slide in which there are 10 to 25 bacilli in each field. Fixing and staining are carried out in the usual manner.

For a period of months all concentrates which were positive in the routine laboratory examinations were reëxamined in the manner described above except those rated as Gaffky I. The results are embodied in table 2.

In examining the slides under the microscope a preliminary inspection

TABLE 2

Some of the results with the proposed method compared to Gaffky count

NUMBER	GAFFKY	DATE	NUMBER OF ACID-FAST BACILLI IN MILLIONS					
14	VII	4/6	53.5	51.2	51.2	46.5		
14		4/12	67.5	69.9				
15	V	4/7	39.5	34.9				
15		4/12	72.2	62.8				
15		4/19	62.8	55.9				
16	IV	4/12	1.8	1.8				
16		4/12	2.2	2.4	2.3	2.5		
16		4/15	1.9	1.9	1.2	1.2		
16		4/16	1.9	2.3	1.4			
17	IV	4/14	2.3	2.3	1.9	2.3		
17		4/15	1.2	1.7	1.9	1.9		
17		4/16	1.9	1.9	1.4	1.4		
18	II	4/15	0.2	0.2				
19	I	4/13	0	0.5	0	0	0.2	0.5
20	II	4/16	6.5	7.0	8.3	7.4		
21	III	4/20	5.6	7.9	7.4	6.0	7.9	
22	X	4/22	167	232				
22		4/25	222	230				
22		4/27	381	385	381	448	495	
25	III	4/28	2.3	1.4				
26	IX	4/30	27.9	27.9				
26		5/6	20.9	29.2	36.4	30.7		
			Much tissue					
27	V	4/30	7.4	6.0				
			Much tissue					
28	II	4/30	0.7	0.6	1.4	0.7	1.4	1.1
29	III	5/6	0.3	0.3	0.4			
30	X	5/6	98.0	98.5	89.5	91.2		
31	VIII	5/13	43.4	43.4	37.2	46.5		
31		5/14	33.3	27.8				
31		5/18	47.8					
			Débris, counting difficult					

TABLE 2—*Concluded*

NUMBER	GAFFKY	DATE	NUMBER OF ACID-FAST BACILLI IN MILLIONS					
32	IV	5/13	7.9	7.5				
32		5/14	5.1	7.0	4.6	4.7		
32		5/19	5.1	4.2				
33	VII	5/13	20.0	23.2				
			Much tissue					
35	X	5/18	14.8					
			Much tissue					
36	V	5/19	9.3					
36		5/26	12.0	11.6	8.3	8.8		
36		6/2	20.8	16.3	20.8	18.6		
38	VIII	5/26	12.0	18.6	11.6	15.6		
39	VII	6/2	23.2	20.8	16.7	15.3		
39		6/4	22.2	23.2	23.2	18.6		
40	II	6/2	0	0.4	0	0		
41	IV	6/9	3.0	3.0				
42	VI	6/5	12.2	9.8				
43	X	6/9	204	183				
		6/16	242	247				
44	VII	6/9	19.8	24.4				
44		6/14	27.9	25.5				
44		6/16	34.0	35.4				
46	VI	6/5	10.7	9.3	11.6			
46		6/16	9.8	9.8	13.4	11.4		
46		6/22	14.4	13.9	17.2	14.9	16.3	
47	V	6/14	2.8					
		6/16	2.8	2.8	2.8	2.3		
48	X	6/16	294	288				
49	IV	6/16	4.4	3.9				
		6/22	1.9	2.8	2.8			
50	VII	6/22	6.5	7.5				
51	IX	6/26	186	195				
52	VII	6/26	25.5	19.0	25.5			
54	X	6/26	222	232				

is made to ensure that there is a fairly even distribution and that the slide is free from clumps of bacilli which in some specimens are especially troublesome. Elastic tissue may enmesh an enormous number of microörganisms and prevent an accurate count, and occasionally bacilli are grouped as if agglutinated. Of the 38 concentrates examined, 3 were found to be uncountable for one of the above reasons.

If the slides were not obviously uneven, two groups each of ten fields were counted. The computation of these results is very simple. The mean of ten fields is determined. If the slide was made with .02 cc. the mean is multiplied by 75; if .04 cc. was used, 37.5 is the factor; if .06 cc. was used 25 is the factor; and for 0.1 cc., 15, which gives the number of microörganisms per microscopical field in 1.5 cc., the volume of the concentrate. The number of microscopical fields in the area on the slides is determined as in the Hughes method by establishing the diameter of the field in use with a haemocytometer and solving the formula $\frac{1}{4} \pi D_2$ for the area of the microscopical field. The area of the slide over which the diluted concentrate is spread is 25.4 mm. $\times$ 15 mm., or 381 sq. mm. $\frac{1}{4}\frac{381}{\pi D_2} = 31046$, the number of microscopical fields per slide. This must of course be determined for each microscope. For simplicity we have used 31,000 so our formula is: Mean $\times$ $\frac{1.5}{\text{amount of material used on slide in cc.}} \times 31{,}000 =$ number of bacilli in sputum. Since the concentrate contained the tubercle bacilli from a 72-hour sample, the result of the formula is in terms of the excretion for that period. It was not converted into 24-hour excretion because we wished to use the Gaffky on these specimens for comparison.

The counts given in table 2 show the number of bacilli in millions as well as the Gaffky count. When there is a marked difference in the number of microörganisms found in two groups of ten fields each or if the mean is not at least three times the probable error, the count was not recorded. All other results are included in this table. When more than two figures are given on the date of initial examination, the counts are figured from different amounts of the digest as was discussed previously. When the specimen was recounted an amount was used which we hoped would give 10 to 25 microörganisms to a field. The figures from such reëxaminations are put opposite the dates on succeeding lines, so figures on the same line were all obtained from slides made from

the specimen on the same date. Comparison between counts made on different days is impossible, as the table indicates. Two processes are evidently taking place in the specimen stored in the refrigerator, one is evaporation and one is autolysis. The results of the evaporation may be seen in the counts made on concentrate no. 14 on April 6 and on April 12. There is a small but definite increase in the number of microorganisms in six days that can only be explained by the loss of liquid. The first warning of autolysis is an abrupt drop in the count with the remaining microörganisms well stained. This may be seen in the counts made on concentrate no. 32. Autolysis is delayed in such concentrates longer than in the untreated sputum. Neutralization of concentrates does not affect the autolysis.

We are aware that some of the figures in table 2 are based on numbers too small to be significant. When a slide upon which 0.1 cc. of digest was spread failed to have sufficient bacilli to be statistically valid, the count was included. Specimens nos. 18 and 19 and several others are of this type.

The results appear somewhat distorted by the large factor employed in the calculations which gives a single microörganism the enormous value of almost a half million when the amount of the slide is 0.1 cc. This has a tendency to magnify differences due only to the operation of the laws of chance and the errors of sampling. While it is true that small variations in the slide count may tend to appear greater when calculated in terms of millions of bacilli per day, it is also recognized that this method cannot and does not represent an exact calculation of the number of microörganisms present in the specimen. It does indicate a range within which the actual count may be presumed to be. The extent of this range and the accuracy of the results may be seen from the several counts made on a specimen under one date.

It will be noted that in three specimens the presence of tissue or debris made counting difficult. At times agglutination was a disturbing factor. In one concentrate it made counting impossible.

Even with the limitations discussed, the technique here described seems to have distinct advantages over the one described by Hughes. The fundamental conception of the number of tubercle bacilli excreted daily would seem sounder than the number excreted per cc. of sputum, and presents a wider application of the method. The concentration of specimens minimizes errors of sampling. The use of previously prepared

slides and pipettes calibrated to deliver varying amounts of material increases both the flexibility and accuracy of the method.

For many years there has been much dissatisfaction with the Gaffky count, but its continued use in spite of criticism shows the importance of the information it was designed to provide. Because of a demand on the part of clinicians and epidemiologists engaged in the study of tuberculosis the Hughes technique was evolved. That the results obtained from its use are not entirely satisfactory is indicated by theoretical considerations and practical applications. It is hoped that the method here described will enable the laboratory to furnish the clinician with an index of infection which will be of value in studying the effect of rest, pneumothorax, and other therapeutic aids upon the course of tuberculosis.

SUMMARY

The method of Hughes for estimating the number of tubercle bacilli in sputum is critically reviewed. A new method is described for approximating the daily excretion of tubercle bacilli in sputum.

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CHRONIC NICKEL POISONING AND PRODUCTIVE MILIARY TUBERCULOSIS

Report of a Case

RAPHAEL POMERANZ

Toxic effects of nickel though well known are of rare occurrence. The cases previously described have been chiefly instances of acute nickel poisoning or patients with eczema and dermatitis following more prolonged exposures. In a recent review of 77 cases of protracted exposure to nickel solutions in chemical factories, Wedroff (1) concludes that the dermatitis is undoubtedly a direct result of the exposure to the metal. These workers become more sensitized while at work; recurrences are common. Wedroff and his associates developed a method of determining the sensitivity of each worker by applying to the skin one drop of nickel sulphate solution of varying strengths. Individuals who are sensitive to a one per cent solution of nickel are, in his opinion, unsuitable for work in that industry. Brandes (2) reported, in 1934, a case of acute nickel-carbonyl poisoning with autopsy and toxicologic findings. In his case the nickel contents of the tissues, lungs and brain were determined by the colorimetric method using dimethylglyoxime. This test is of sufficient sensitivity to reveal the presence of .001 per cent of nickel. In Brandes's subject, the extract from 3 gm. of lung gave a bright red color; 3 gm. of brain tissue gave a weaker color which was still a definite red. The same test applied to brain tissue obtained from a case of meningitis gave no color reaction.

Armit (3) many years ago studied the toxicity of nickel compounds experimentally. More recently Hendrych and Escobar-Bordoy (4) described the effects of the intravenous injection of nickel compounds in rabbits; the injection produced central paralysis, degenerative changes, oedema and haemorrhages in the heart, lungs, brain and parenchymatous organs. They attribute the parenchymatous changes to vascular narrowing.

Our case differs from those above cited, by its unusual history, its complication with a slowly progressive type of productive miliary tuber-

culosis and by the fact that it puzzled a number of experienced investigators until after the necropsy and toxicologic data had been obtained.

Case Report

I. *J.*, a 22 year old white man, had been working as an industrial chemist in a laboratory for the last six years. In his work he used many metallic elements such as mercury, antimony, zinc and lead. In the last two or three years, he worked with radio tubes which contained almost ninety-nine per cent of nickel. His work required him to place large pieces of nickel in a container; he then poured carbon-tetrachloride solution over the metal and boiled it to separate the grease. While boiling, he would stand over the container, and stir the solution; at this time he was exposed to the fumes. He repeated this procedure several times each week. On September 25, 1935, he came to my office for an X-ray examination of the chest, referred by Dr. B. Silverstein. The chief complaint was shortness of breath on exertion. He reported extensive loss of weight and appetite in the last few weeks. There was some nonproductive cough and he suffered from transient pains in the chest. The patient said that he had suffered from the "grippe" during the last two weeks, and some rise in temperature, but that he had had no other symptoms of importance. His family and childhood history was negative for serious illness or tuberculosis.

Radiographic findings on September 25, 1935 (figure 1): The thorax is symmetrical, the intercostal spaces are even. Throughout both lung fields fine nodular infiltration, millet in size, can be noted. These nodules are so thickly distributed that the lung markings are practically obliterated. They are more densely distributed in the upper lung fields. The hila are hazy, partly fused with the cardiac borders which are obscured. The trunk shadows cannot be recognized. The diaphragms showed poor motion. The patient was reëxamined seven days later, October 2, 1935 (figures 2 and 3) at which time no material change could be noted.

On October 21, 1935, the patient entered the New York Hospital where he remained for several weeks. The summary of the findings on his discharge on December 2, 1935 was made by Dr. N. Plummer as follows: Patient states that three months ago he developed a dull aching pain behind the sternum which was aggravated by deep breathing. About one month after this he noticed some shortness of breath. These symptoms gradually became more noticeable and extreme dyspnoea developed on slight exertion. About two weeks before admission he developed a dry hacking cough, which was also aggravated by deep inspiration. At the beginning of his illness he began to lose his appetite and gradually lost 30 lbs. in weight. During the last two months the patient was constantly in bed under medical care.

Tonsils were hypertrophied. Slight bilateral enlargement of the lymph

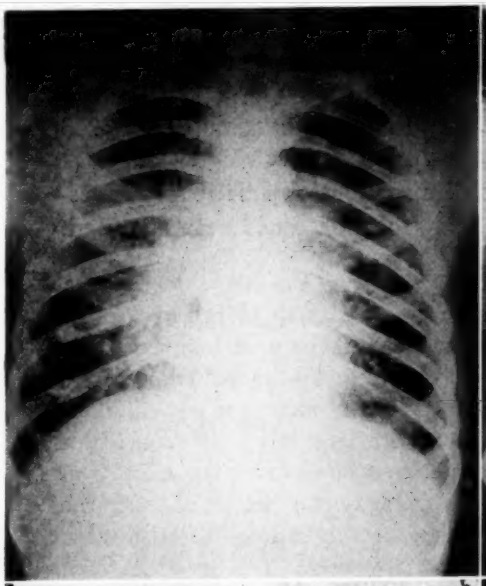

FIG. 1

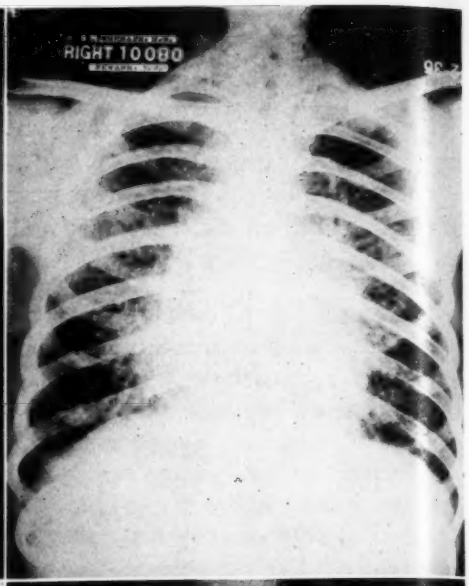

FIG.

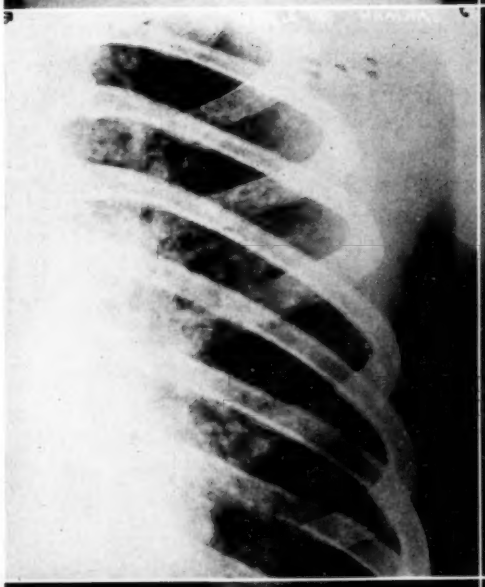

FIG. 3

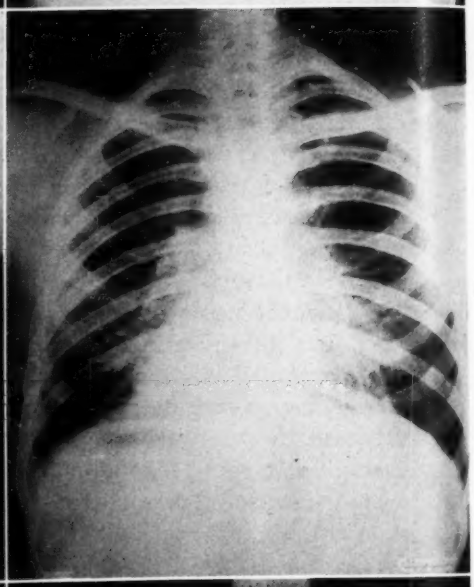

FIG.

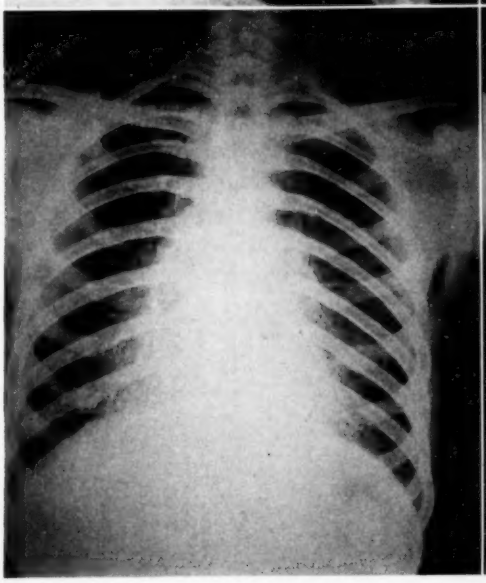

FIG. 5

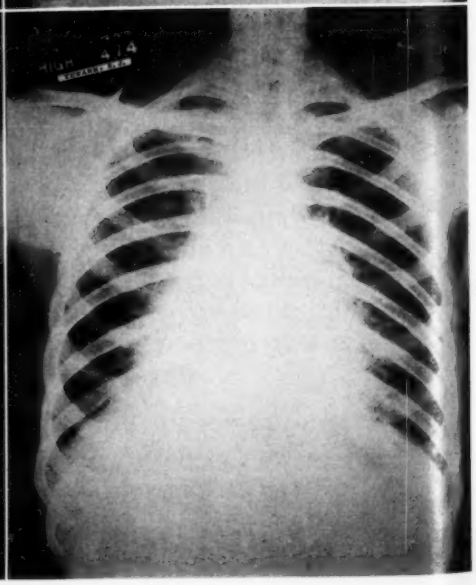

FIG.

nodes at the angle of the mandible was noticed. He exhibited very slight cyanosis of the lips and tongue. Heart findings were not unusual and there were no cardiac murmurs. The abdominal muscles were tense due to the dyspnoea. The liver could be palpated one finger's depth below the right costal margin. Over the right lung anteriorly there was dulness throughout with increased vesicular and bronchial sounds in the upper and lower third. Râles were audible in the lower third. Posteriorly, dulness, increased vesicular and bronchial sounds in the lower third anteriorly and posteriorly were noted. The patient exhibited clubbing of the fingers and cyanosis of the nails.

Urinalysis was negative. The blood count numbered 4,200,000 red cells, 9,200 white cells, while the haemoglobin was 90 per cent. Of the leucocytes 52 per cent were adult and 22 per cent were immature. The lymphocyte proportion was 19 per cent, monocytes 2 per cent and eosinophiles five per cent. On discharge the blood count was 4,200,000 red cells, 5,000 white cells, the haemoglobin was 85 per cent. Of the leucocytes 47 per cent were adult, and 21 per cent immature. The lymphocytes were 17 per cent, monocytes 9 per cent, eosinophiles 5 per cent and the basophiles 1 per cent. The blood Wassermann test was negative. Urea nitrogen was 10, blood cholesterol 211, and the icteric index 5.4.

The sputum was repeatedly negative for acid-fast bacilli. The intracutaneous tuberculin reaction was negative up to one milligram.

X-ray of the chest showed bilateral enlargement of the hilar shadows with an indefinite border. Scattered throughout both lungs there was a uniformly increased density of rather soft fine mottling. No confluence and no evidence of calcifications or cavitations were seen. The impression was that of a typical form of miliary involvement with a possibility of dust infection or of the dissemination type of lymphoblastoma. In the oblique views there was considerably increased density in the posterior mediastinum. At the time of discharge the density of each hilum was definitely less marked both in character and extent than on admission. There was also some diminution of the markings of the parenchyma of the lungs.

FIG. 1. September 25, 1935. Shows advanced interstitial and miliary nodular infiltration, discrete in type, with some involvement of the hilar and mediastinal lymph nodes. Emphysema at the bases.

FIG. 2. October 2, 1935. No material change from fig. 1.

FIG. 3. Enlarged upper half of the right side of fig. 2 showing the pulmonary nodular infiltration more in detail.

FIG. 4. February 3, 1936, showing marked clearing up of the lung field resulting from regression from the infiltration in the periphery of the chest.

FIG. 5. April 25, 1936. Recurring infiltration spreading from the hila again to the periphery in the form of bands and some nodulations.

FIG. 6. July 22, 1936. Ten days before death, showing further progress in the above described infiltrating process.

He continued to cough and was very dyspnoeic on the slightest exertion. For a differential diagnosis, a biopsy of a right supraclavicular lymph node was attempted, but no nodule could be found. As it was felt that the pulmonary condition was either a fibrosis due to chemical irritation or some form of lymphoblastoma, a therapeutic test of X-ray treatment was made. Two days after the first treatment his temperature dropped to normal and remained normal throughout his hospitalization. He received thirteen X-ray treatments of 200 R units each. During the treatment he lost his appetite and was markedly nauseated and vomited frequently. This, it was felt, was due to the radiation. Gradually the dyspnoea decreased and the cough disappeared and the patient was finally able to move about and exert himself with comparatively little discomfort. The sputum averaged about 20 cc. each day during his stay. His weight remained substantially the same, 52.5 kilograms. The physical signs in the chest remained about the same, but the cyanosis of the finger nails improved shortly after X-ray therapy had been instituted. X-ray of the chest on discharge showed some clearing of the pulmonary process. Vital capacity had increased to 2,800 cc.

The patient was X-rayed again on February 3, 1936, by Doctor Plummer (figure 4). This film showed much less nodular infiltration; the hila were clearer; the pulmonic markings were less dense; the aeration of the lungs was better. He felt better clinically. The dyspnoea, though slightly alleviated, was still pronounced on exertion. He returned to me in April, 1936. The film taken at that time (figure 5) again showed increased cloudiness of the cardiac borders and of both hila; the pulmonic markings were more pronounced than on the film taken in February, 1936. They had more the appearance of bands forming a fine network and obliterating the vascular structure of the lungs. He was examined again on July 22, 1936 (figure 6). He still complained of dyspnoea and in spite of complete rest he did not gain weight. The radiographic examination revealed further increase in the density of both hilar shadows and of the trunk shadows which completely obliterated the cardiac borders. The pulmonic markings at the periphery were also completely obliterated and many discrete coalescing nodulations could be seen in the apices and in the peripheral parts of the lung fields. Patient died about ten days later with the symptoms of a coma resembling a heat stroke after an excessive exposure to sunshine at the seashore.

Autopsy findings by Dr. H. S. Martland: This male white body 5 feet 2 inches high, weighed about 115 lbs. No lymph nodes were palpable. The fingers were distinctly clubbed and slightly cyanotic.

Abdomen: The diaphragms were ballooned down between the sixth and seventh ribs on each side. The abdominal viscera were otherwise in normal position though slightly pushed downward. The great omentum contained atrophic fat. In the mesentery of the small intestine, three calcific glands,

.5 to 2 cm. in size, were seen. There were about two ounces of amber clear fluid in the pelvic cavity.

Thorax: A small amount of fresh fibrinous gelatinous exudate was seen over the left lung. There were no adhesions in the left pleural cavity. No fluid was found in the right pleural cavity but there were a few old adhesions at the apex. The thymus was replaced by fat. The anterior border of the lungs reached to within two and a quarter inches from the midline as measured opposite the third rib. The sternum was free. The lungs were retracted exposing most of the precordium. The apex of the heart lay in the fifth interspace at the midclavicular line.

Heart: There was a distinct hypertrophy of the right heart, especially in the conus. The right ventricle in the conus measured about three-eighths of an inch in thickness. The endocardium and the valves were free. The left heart was not hypertrophied and its endocardium and valves were free. The aorta was elastic and free with an occasional streak of soft atheroma.

Left lung: The large bronchus was of normal size and free of exudate. Its mucosa was smooth, pale and firm. The peribronchial nodes were moderately enlarged, slate colored with very little anthracosis and no calcifications. The lung felt very tough and leathery; the visceral pleura, in its dependent portions, as thickened and opaque. A fine nodular, granular surface was felt over the entire pleura and lungs. Over the lower lobe could be seen with the naked eye some slightly grayish, miliary elevations 1 and 2 mm. in size over the pleura. On section the lower lobe was dark red, tough and leathery; diffusely scattered over the entire lobe were very small grayish miliary masses which were not confluent. The small bronchi contained no pus. The upper lobe exhibited the same appearance as the lower lobe.

Right lung: The right lung in general resembled the left. All three lobes were involved with a few emphysematous bullae at the apex. The lung was heavy.

Spleen: The spleen was of normal size and conformation and its capsule was free and clear. On section it was dark red, its lymphoid tissue being hardly visible, but firm.

Liver: Total width of liver was 10 inches. Right lobe measured 7 inches. On section the liver was dark brownish ochre in color with a distinct nutmeg appearance.

Head: The pia-arachnoid over the top of the brain was free. The gray matter was normal, brownish in color and the vessels at the base were free. There were no tubercles. The lateral ventricles, the basal nuclei and all the structures at the base of the skull were free and clear.

Histological findings: (figures 7, 8 and 9) Lungs: Throughout both lungs there was evidence of numerous small miliary nodulations most of them single, scattered diffusely throughout the parenchyma. Most of the nodules showed

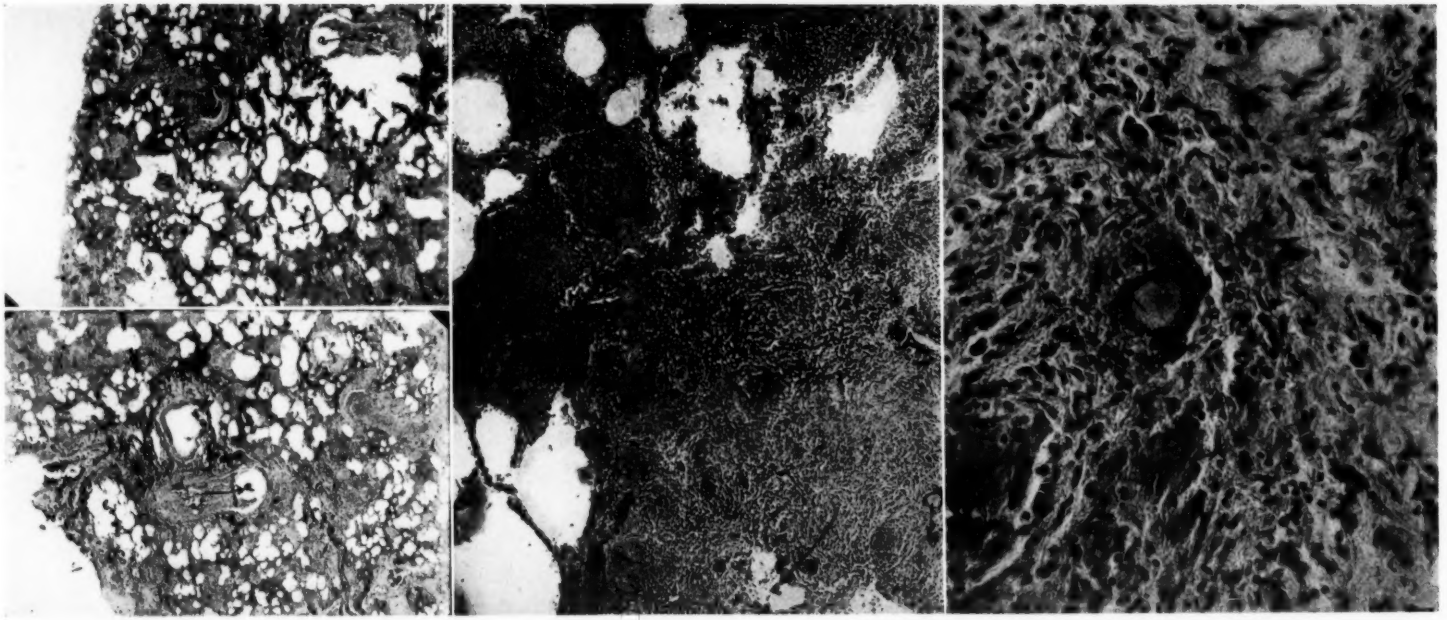

FIG. 7 FIG. 8 FIG. 9

FIG. 7. Photomicrograph. Low power. Presenting a general view of the pulmonary pathology. Irregular distributed nodulations (a) showing central necrosis; (b) thickened interstitial septa. In some places widened (c) emphysematous alveoli.

FIG. 8. Photomicrograph. High power of the tuberculous granulation tissue consisting of (a) epithelioid and some (b) giant cells.

FIG. 9. Photomicrograph. High power, large magnification, showing centrally a giant cell (a) surrounded by (b) fibroblasts and (c) epithelioid cells.

the characteristic structure of miliary tuberculous infiltration, consisting of epithelioid cells, occasional giant cells, but few lymphoid cells. In some places there were oedema and congestion. In other places, the nodules were situated in the parenchyma surrounded by emphysematous alveoli. The interstitial septa of the lungs throughout were thickened. Perivascular and peribronchial hyperplastic changes were also noticeable in the vicinity of the miliary nodules. In the centre of some of the nodules there were areas of hyalinized necrosis.

Spleen: The spleen gave evidence of hypoplasia of lymphoid follicles with occasional miliary tuberculous nodules and congestion.

Liver: The liver showed evidence of chronic passive congestion with occasional early tuberculous nodulations, chiefly of epithelioid cells.

Toxicologic findings: The toxicologic examination of the lungs reported by Dr. A. E. Edel and J. P. Brady, Chemists, showed that the right lung weighed 675 gm. and the left 795 gm.

	Right lung	*Left lung*	*Both lungs*	*Lungs from drowning case for comparison*
Weight received for examination	285 gm.	290 gm.	235 gm.	410 gm.
Extracted	27 gm.	47 gm.	44 gm.	58 gm.
Ash	1.575,5 gm.	1.704 gm.	1.661 gm.	1.534,5 gm.
Per cent nickel in ash	0.172	0.155	0.173,7	None
Per cent silica ash	2.08	2.08	2.08	2.19

The chemical analysis revealed the presence of nickel in all parts of the lungs. There was 0.17 per cent nickel in the ash which was brownish-red in color. The presumption of nickel was indicated by the color of ash and by the positive reaction of the ashed lung with dimethlglyoxime; 1.5 gm. of the ashed lung gave a pink color reaction. Normal lung contains no nickel. The ash of the lung obtained from the drowning case, examined for comparison, was grayish-white in color. The samples from both showed normal amounts of silica.

DISCUSSION

The diagnosis of nickel poisoning was made on the basis of the toxicologic findings. It was only after this diagnosis was suggested by these data that we investigated the background of the patient and secured from the father the history of exposure to nickel fumes.

Reviewing the case, one realizes the diagnostic difficulties. It seems to me, however, that the diagnosis of productive nodular tuberculosis could have been made *intra vitam*. The first film taken September 25, 1935 was sent to Doctor Pancoast of Philadelphia with a short descrip-

tion of the history and occupational exposure. Doctor Pancoast suggested in his reply that while he could not make a positive diagnosis from one film he was thinking of tuberculous mediastinitis and suggested serial radiographic examination. The other investigators who saw the case gave various opinions, and bronchiolitis obliterans, miliary type of pulmonary Hodgkin's disease, carbon tetrachloride poisoning. The last opinion was also voiced by an expert toxicologist. Lowy (5) discussing 20 cases of chronic carbon tetrachloride poisoning stresses the fact that practically all the workers showed evidence of functional liver damage proved by positive liver galactose tests (excessive excretion) and the presence of urobilinogen in urine. Our subject had a nutmeg liver evidently due to chronic congestion; no galactose tests of the liver were performed *intra vitam*; urine showed no evidence of urobilinogen. However, the entire clinical picture, as we now see it, spoke against carbon tetrachloride poisoning. These tests if done could have definitely excluded chronic carbon tetrachloride poisoning.

My opinion was that we were dealing with a case of interstitial type of infiltration and nodulations resulting from some occupational exposure evidently not silica. The return of the discrete nodulations a few months after radiation should have made one realize that this was a case of a slowly progressing type of productive nodular tuberculosis.

Considering the history, together with the histological and toxicologic findings, it is difficult to explain the pathogenesis of this condition. The probable explanation is that the patient had a latent tuberculous lesion. As a result of exposure to chemical irritants such as nickel, various degrees of inflammatory reactions ensued in the lungs. These, in turn, activated the tuberculous focus which spread slowly along the lymphatics. From experimental work we know that the nickel gets into the blood-stream in form of a colloidal compound. As such, it is extracted from the blood-stream by the reticuloendothelial cells of the entire body, chiefly those of the liver, spleen, lungs, lymph nodes and bone marrow. We also know that the reticuloendothelial system plays a large rôle in producing immunity and in fighting off the tuberculous infection. It appears to me that it was the interplay of the two factors, of a colloidal poison and a tuberculous infection, which produced so unusual a type of histopathological and toxicologic findings. Of course it is difficult to say which factor was more powerful.

One might ask what effect the nickel had on the pulmonary parenchyma. Why did the productive nodular tuberculosis spread so slowly?

These questions are difficult and probably impossible to answer. We are inclined to believe that the nickel helped to produce the interstitial fibrosis. The nodular tuberculosis spread slowly. One might be able to reconstruct the development of these nodules from the time when they slowly began to recur about two months after radiation. They appeared in a discrete form, spreading slowly, near the lymphatics, finally becoming so numerous that the aggregate of the nodules and the interstitial fibrosis resulted in marked impairment of the vital lung capacity and caused death by the collapse of the right heart.

SUMMARY AND CONCLUSIONS

A case of chronic nickel poisoning and productive miliary tuberculosis is reported together with serial radiographic, microscopical and toxicologic findings. *Intra vitam* the diagnosis was not made and the radiographic findings were misinterpreted. An attempt was made to explain the pathogenesis of the condition. The case also suggests that nickel inhaled in small amounts over a long period of time may produce disastrous results when combined with another chronic progressive type of pulmonary disease. This might be important as a hazard in the nickel industry.

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CYSTIC DISEASE OF THE LUNGS[1]

JAMES L. DUBROW[2] AND W. R. WYNNE[2]

Cystic disease of the lung (synonyms: congenital cyst of the lung, polycystic disease of the lung, air cyst of the lung, cystic emphysema, bullous emphysema) has caused considerable discussion in recent medical journals; the various synonyms denote disagreement concerning the aetiology and some confusion as to whether there is such a clinical entity. The question of the aetiology of cystic disease of the lung (congenital or acquired) may be left open for later settlement when much more detailed histopathological study is available. An agreement may be reached, however, on clinical grounds as to which patients, presenting signs of spontaneous pneumothorax (localized or generalized), with the X-ray showing only an area or areas of decreased density with no evidence of pulmonary collapse or multiple cyst-like dilations of the bronchi with thin walls, plus secondary atelectatic effect, may have cystic disease of the lungs.[3] Such tentative diagnosis (cystic disease of the lung) will be more likely to prove correct if the condition is detected early in life, preferably in infancy. However, the age of the patient is not necessarily an obstacle in making such a diagnosis as may be shown by the following case.

Case Report

White male, Register No. 5297, age 40, weight 137 pounds, height 5 feet 5½ inches, farmer by occupation, ambulant, was admitted to the Veterans Administration Facility, Des Moines, Iowa, September 9, 1936, for treatment of spontaneous pneumothorax, right, complete, old; pleurisy, subacute, right; and emphysema, chronic, left. It should be noted that this patient was previously examined by the Veterans Bureau on December 23, 1932, at which time a diagnosis of pneumothorax, right (probably permanent), cardiac displacement secondary to the pneumothorax, and bronchitis, chronic, was made. The report of the X-ray film of the chest made on that date (December 23,

[1] Published with the permission of the Medical Director of the Veterans Administration who assumes no responsibility for the opinions expressed or the conclusions drawn by the authors.

[2] Veterans Administration, Des Moines, Iowa.

[3] See suggested classification of cystic disease of the lung by one of the authors (1).

1932) stated that there was a collapse of the right lung with the exception of a small portion of the upper part of the right upper lobe, apparently due to a pneumothorax, that the heart and aorta were drawn to the left, and that the left lung showed disseminated fibrosis.

The family history was unimportant. Patient stated that he had been under a doctor's care at various times for lung trouble, that he was hospitalized during the World War in France for sixteen days with bronchopneumonia. The patient attributed his present symptoms, pain in his right lower chest, soreness in his right lung and shortness of breath, to his attack of bronchopneumonia while in service. No history of haemoptysis or cough was elicited. Physical examination showed the following abnormal findings: The right hemithorax seemed larger than the left, expansion was definitely limited on the right side, and there was a hyperresonant note bordering on tympany through the right lung; the breath-sounds were audible but diminished at the right upper apex and infraclavicular region, second to third interspace, while through the remainder of the right lung the breath-sounds were greatly diminished or absent. Left lung was negative. Cardiac examination was negative. Blood-pressure was 118/90; pulse 84.

Stereogram of the chest showed absence of lung markings through the right lung field with the exception of a few striations (bronchial at right lower base), and the visceral pleura was not visualized as it would have been in a large pneumothorax (figure 1). An intratracheal lipiodol injection with patient lying on his right side was made; the lipiodol largely failed to enter the right lung, and most of the lipiodol entered the left bronchus as visualized on the fluoroscopic screen and checked subsequently by chest roentgenogram (figures 2 and 3), thus suggesting atresia of the right bronchus with associated cystic changes of the right lung. A bronchoscopic examination was then made by Doctor Mumma which showed "the left main stem bronchus leaving the trachea at the normal angulation. There appeared to be practically a complete atresia of the right main stem bronchus, only a small slit-like indentation was present where the normal bronchus should continue from the trachea. There was a complete absence of any inflammatory change as well as any obstruction such as might occur from a new growth formation. The carina had the appearance of marked thickening and induration. There is no pathological change noted in the left bronchus. It is quite likely that the condition is one of congenital origin."

A diagnostic pneumothorax, right, was made with an initial reading of minus 1 plus 1. After 50 cc. of air, it was zero plus 1; after 200 cc. of air, plus 1 plus 2; after 350 cc. of air, zero plus 3; after 450 cc. of air, zero plus 3. No pain was experienced by the patient. X-ray films taken after inducing pneumothorax showed air in the right pleural cavity and the visceral pleura of the right lung as well as the partially collapsed pulmonary structures were

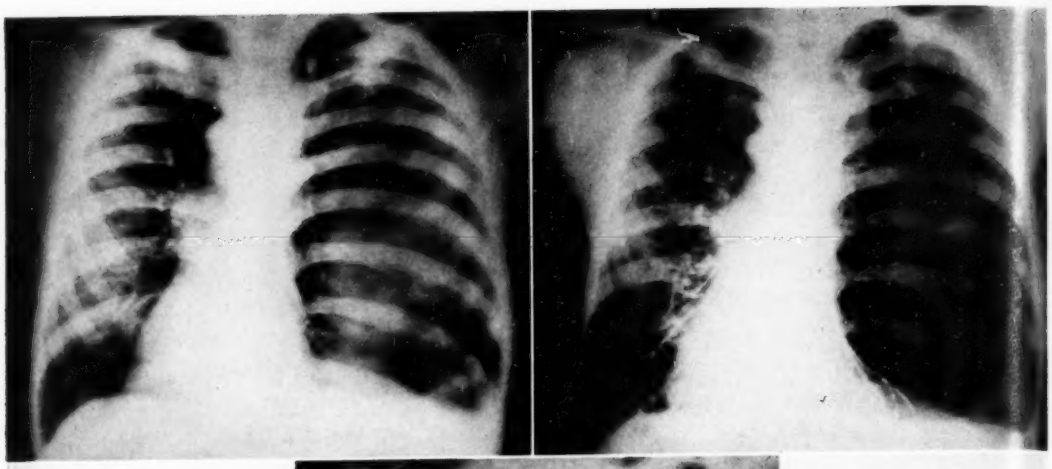
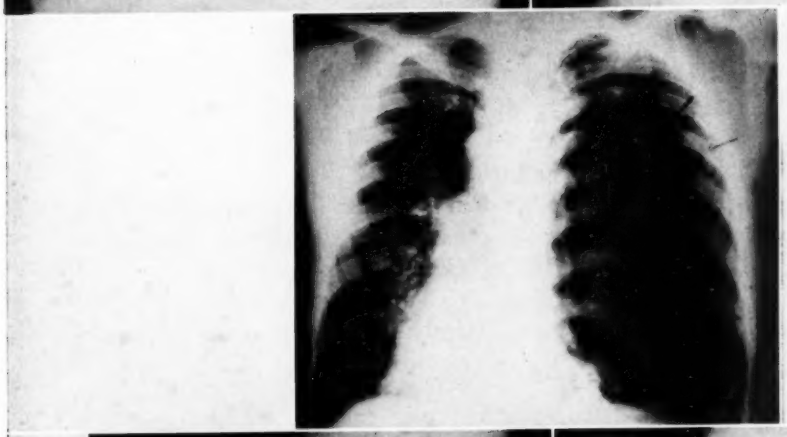


FIG. 1



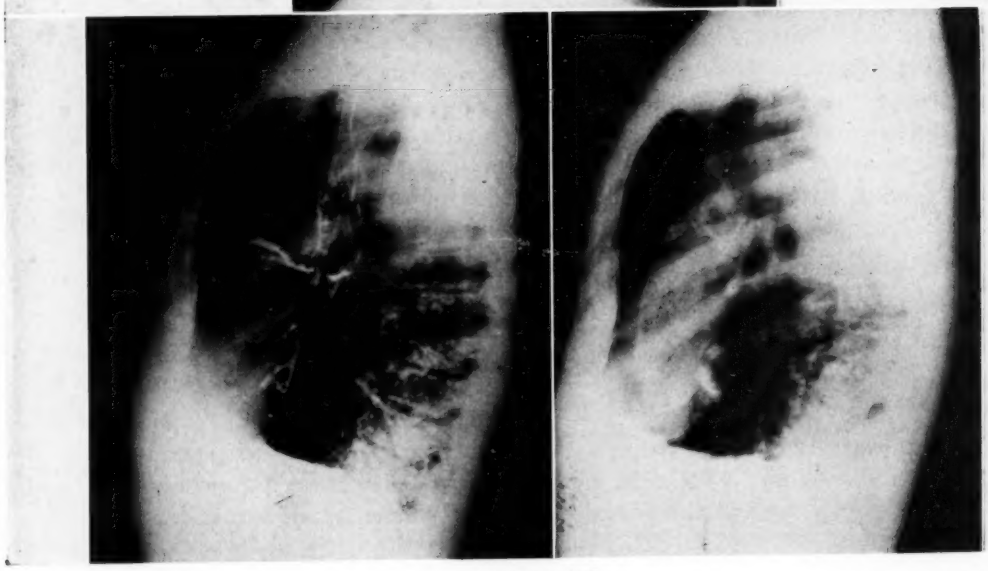


FIG. 3

FIGURES 1–5

visualized (figures 4 and 5), thus ruling out the admission diagnosis of spontaneous pneumothorax. Patient's temperature, pulse and respiration during his stay in the hospital were within normal limits and his expectoration was slight and persistently negative for tubercle bacilli. He showed only slight shortness of breath and he was discharged October 13, 1937 with a diagnosis of cystic disease of right lung.

FIG. 1. Admission roentgenogram of chest shows right lung of increased transparency and larger than the left. No pulmonary or bronchial markings are visualized in the right lung field, except perhaps at right upper apex and right lower base. The left lung shows normal parenchymal markings. Right dome of the diaphragm is on a lower level than the left. Heart is deviated to the left.

FIG. 2. After lipiodol injection. The bulk of the lipiodol is seen in the left lung with only slight scattering to right lower and upper lobe bronchi, although caution was taken to have patient lie on his right side during the intratracheal injection.

FIG. 3. The lateral film shows slight lipiodol filling of right middle lobe bronchus and a small amount in the bronchi of the upper right lobe and right base, with the bulk of the lipiodol in the left lung.

FIG. 4. Pneumothorax induced, right. The visceral pleura and the partially compressed intrapulmonary hollow spaces are outlined.

FIG. 5. Lateral view in confirmation of interpretation of fig. 4.

CONCLUSION

We think it is not unimportant to report this case because of the confusion of cystic disease of the lung with pneumothorax, which diagnosis this patient carried for a long period. Radiographically, it is of paramount importance when an X-ray diagnosis of pneumothorax is made that the visceral pleura be visualized. If this structure is not shown on stereoradiograms presenting areas of decreased density or increased transparency, cystic disease of the lung should be considered. A diagnostic pneumothorax, bronchoscopy and lipiodol injection may have to be resorted to in order to clinch the diagnosis as in the case reported.

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PULMONARY GANGRENE COMPLICATING PULMONARY TUBERCULOSIS[1,2]

Case Report

EVERETT K. GEER

This case is reported because of a dearth of similar instances in the American literature as pointed out by Murray (1). The interesting points in the case to be presented are: (*1*) the unusual association of the two diseases, (*2*) the dramatic change in the clinical picture with the supervening gangrene and the swift, fatal termination, (*3*) the ineffectiveness of therapy, (*4*) the dissemination of the tuberculosis.

Case Report

J. P., a single male, aged 41, a laborer, was admitted to Ancker Hospital on January 28, 1936. His family history revealed no tuberculosis nor was there any known contact. His past history revealed nothing important.

He complained that he had had frequent "chest colds" for some time and began to cough more about eight days before admission to the hospital. The cough was slightly productive. For four days preceding admission to the hospital he had been weak and tired more easily than usual. He had had night sweats for a week before admission to the hospital and was chilly the night before admission but did not know if he had had any fever.

Physical examination revealed a well developed, well nourished male, not acutely ill in appearance. His temperature was 102°F., pulse 80 and respirations 18. His mouth disclosed marked oral sepsis. His chest revealed dulness with moderately coarse râles to the second rib and sixth dorsal spine on the right. The left lung was clear. His physical examination was otherwise negative.

Laboratory examinations showed a faint trace of albumin in the urine; haemoglobin, 77 per cent; red blood cells, 4,190,000; white blood cells, 7,650 with 68 per cent polymorphonuclear neutrophiles; 20 per cent lymphocytes; 9 per cent monocytes; 2 per cent eosinophiles; 1 per cent basophiles. The blood Wassermann was negative. The sedimentation rate was 79 mm. in one hour. The sputum revealed tubercle bacilli on microscopical examination.

[1] From the Tuberculosis Department, Ancker Hospital, St. Paul, Minnesota.

[2] Presented at a meeting of the Minnesota Society of Internal Medicine, Duluth, Minnesota, June 6, 1936.

Roentgenograms of the chest showed a parenchymal infiltration in the right upper lobe with cavitation.

The diagnosis was pulmonary tuberculosis, moderately advanced "C."

On January 31 he was restless and irrational with hot, dry skin and continued so. On February 3, early in the morning he had a very severe coughing spell and raised some thin, purulent, rusty sputum. Later the same morning after another severe coughing attack he raised foul sputum and it was noticed, with unproductive cough, that his breath was fetid. Sputum examination

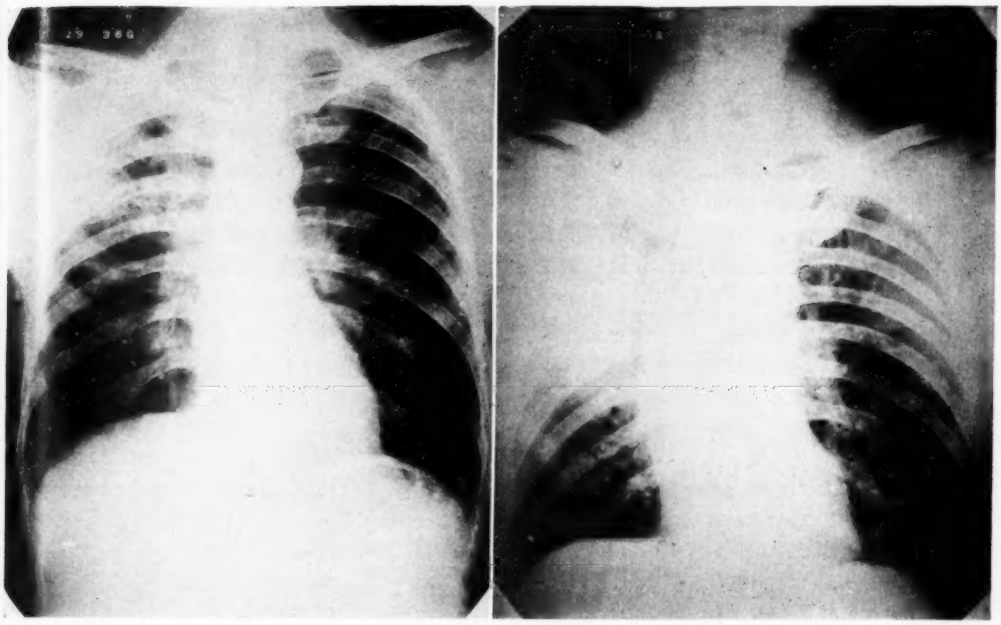

FIG. 1 FIG. 2

FIG. 1. Case *J. P.* January 29, 1936. Right upper lobe infiltration with cavitation.

FIG. 2. Case *J. P.* February 10, 1936. Upper half of right lung now homogeneously dense.

now revealed tubercle bacilli, Vincent's spirochetes and fusiform bacilli. Repeated examinations of the sputum confirmed these findings.

Intravenous arsphenamine was begun. On February 3, .1 gram; February 5, .6 gram; February 7, .6 gram; February 10, .75 gram; February 13, .75 gram were given. Diarrhoea ensued and arsphenamine was discontinued. Fluids were forced and general supportive measures employed. On February 8 he became somewhat cyanosed and was put in an oxygen tent.

On February 10 a bedside chest roentgenogram showed a marked density in the upper two-thirds of his right lung; his white blood count was 25,500

and his sedimentation rate 111 mm. in one hour. He was still acutely ill and continued to raise thin, purulent, fetid sputum. Artificial pneumothorax was attempted on the right but no pleural space was found.

He died on February 18, 1936, twenty days after admission.

Postmortem examination, aside from the thorax, revealed little of note. There was cloudy swelling of the heart, liver and kidneys in addition to an acute splenitis.

On opening the thorax the left lung was found to be adherent to the lateral chest-wall by a single fibrous tag. The left pleural cavity was empty. The right pleural cavity was completely obliterated by firm, fibrous adhesions. The right lung weighed 1,985 grams. The pleural surface was covered with fibrous adhesions and the lung was considerably mutilated in removal. The cut surface of the lung showed the entire lower lobe to be filled with clusters of miliary, grayish-white nodules. These had the appearance of a tuberculous process. Almost the entire upper lobe was gangrenous and contained a large, irregular, multilocular cavity. This lesion extended to some degree into the middle lobe. The gangrenous lung was foul smelling and the lung showed an additional small cavity in the base of the upper lobe measuring about 1.5 cm. in diameter. The lung tissue outside of the nodular area and the cavity described showed a marked excess of fluid. The hilar nodes were enlarged and oedematous and contained miliary nodules. The left lung weighed 1,175 grams. The pleural surface was smooth and crepitation was reduced throughout the lung. On cut section the entire lung was found to contain an excess of blood and fluid. Throughout the lower lobe there were numerous miliary grayish nodules most pronounced in the basal portion of the lung. The bronchial tree contained purulent material and it was thought that some of the grayish area might be pneumonic areas of consolidation though most of them looked like miliary tubercles.

Smears from the gangrenous area of the lung at autopsy showed Vincent's spirochetes, fusiform bacilli and tubercle bacilli.

Microscopical examination of sections of the lungs showed in certain areas many of the alveoli filled with fibrin and acute inflammatory cells. In other areas the alveoli contained only scattered polymorphonuclear leucocytes while in still other areas the alveoli were filled with serum. At certain points in the lungs the sections showed a necrosis of the lung tissue with the structures remaining. The alveoli were outlined by pink-staining homogeneous masses representing shadows of the tissue. There was no evidence of an inflammatory reaction in these zones. In other sections the lung tissue showed definite areas of localized caseation necrosis. Some of these showed typical Langhans' giant cells at their margins but for the most part there was no evidence of an epithelioid reaction around the tubercles and no typical zone of lymphocytes was seen. Certain of the caseous nodules showed a dense polymorphonuclear

infiltration. Other tubercles were fairly typical with caseous centres and surrounding fibrosis with typical Langhans' giant cells.

The balance of the tissues showed nothing of note. There was no evidence in the other organs of a tuberculous process.

CONCLUSION

A case is reported of manifest moderately advanced pulmonary tuberculosis with supervening gangrene which went on to rapid, fatal termination with dissemination of the tuberculosis despite intensive treatment for the gangrenous process.

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MANTOUX TESTS WITH THE GOTTSCHALL-BUNNEY DILUENT FOR TUBERCULIN[1,2]

A Report of 1,648 Tests

EMILIE CLARKE

Many comparative studies of tuberculin tests have been carried out by various observers in an effort to find the most efficient and sensitive method. Although the results have been varied, it is now generally acknowledged that the Mantoux test is the most delicate and accurate (1, 2, 3, 4, 5).

The chief objections to its use are that diluted Old Tuberculin may lose its potency rather rapidly with age and its dilution requires a specially trained technician (6). In an effort to overcome this, Gottschall and Bunney (7) devised a special diluent, in which they hoped tuberculin would retain its potency for a reasonable length of time. If satisfactory, this diluent would enable the manufacturer to dilute the tuberculin ready for use before distribution. The manufacturer could then test the diluted tuberculin for potency and sterility. All using the product would thus be assured of a standard, uniform preparation, safe and easy to use.

EXPERIMENTAL

One thousand six hundred and forty-eight tests were performed on white and colored patients in the outpatient tuberculosis clinic at Herman Kiefer Hospital. The usual procedure in this clinic was to test only children and young adults up to and including the age of twenty. Upon special request some from older age groups were included. All new admissions were routinely tested with a 1:10,000 (0.1 cc. = 0.01 mg.) dilution of Old Tuberculin, followed if negative by a 1:100 (0.1 cc. = 1 mg.) dilution. Old cases with previous negative tests and new cases with negative Pirquet tests were retested with the 1:100 dilution. The

[1] This paper covers in part the dissertation submitted to Wayne University College of Medicine by Emilie Clarke as partial requirement for the degree of Doctor of Public Health.

[2] This study has been carried out in collaboration with Dr. C. C. Young and Dr. W. E. Bunney of the Bureau of Laboratories, Michigan State Department of Health.

testing was supplemented by X-ray examinations of the positive reactors. Special requests on the part of referring physicians, or whenever clinic physicians thought there was some indication for it, resulted in many nonreactors being X-rayed. A few patients with records of positive reactions to tuberculin tests in former years (1918–1936) were included as a recheck of old reactors and to see the effect of the tuberculin in this diluent on known reactors.

Diluents: The diluent for the tuberculin used in these tests was prepared according to the formula of Gottschall and Bunney (7).[3] Tuberculin in this diluent will hereafter be referred to as "ready diluted tuberculin." It was supplied in 10 cc. vials in the 1:10,000 and 1:100 dilutions, which, except when in use, were kept in a drawer a foot from a steam radiator during the entire period of testing. Fresh dilutions of International Standard and of the tuberculins used in the diluent were used as controls. These were freshly prepared in physiological saline once a week and kept in the ice box when not in use.

Method of testing: Each person tested was given an intracutaneous injection of 0.1 cc. of the ready diluted Old Tuberculin on the right arm and 0.1 cc. of freshly diluted tuberculin on the left arm. The injection was made on the flexor surface of the forearm just below the bend of the elbow (8). The patients were asked to return on the fourth day for the readings. Some were tardy in returning and a few were read in homes by nurses where they had permission to call. The tests were measured in the transverse diameter only. Readings were made on the fourth day rather than in the customary 24- and 48-hour interval because the fourth day reading has long been standard procedure in this clinic. Since the testing in this paper was part of the routine testing in the clinic for the duration of the study it was felt best to conform with the clinic practice. The period of testing was from December 15, 1936 to March 13, 1937.

TESTS WITH THE READY DILUTED 7H AND INTERNATIONAL STANDARD

With the 1:10,000 ready diluted 7H (Michigan Department of Health) and International Standard (Medical Research Council), 138 persons were tested. Of these, 39 were positive. In 15 there was a difference of from 1 to 3 mm. in the size of the reactions on the two arms. In 8 the reaction was larger on the arm injected with the International Standard,

[3] 0.04 per cent gum arabic in borax, boric acid, saline solution, pH 7.2, phenol 0.5 per cent.

while in 7 the ready diluted was the greater. With the 1:100 dilution 37 were tested and 12 found to be positive. Of these, 6 had reactions of the same size and intensity, while of the remaining, 5 had variations of from 2 to 5 mm. and 1 of 10 mm. in favor of the International Standard.

Of the 138 tested with the ready diluted 7H and International Standard 1:10,000, 22 previously recorded positive reactors (1924–1932) were tested. Of these, 19 reacted to the 1:10,000 dilutions on both arms, one was negative to the 1:10,000 but positive to the 1:100 while 2 were negative to both dilutions.

TESTS WITH THE READY DILUTED 7H AND FRESHLY DILUTED 7H

One hundred and sixteen tests were performed with the 7H ready diluted, using the freshly diluted 7H as a control in the 1:10,000 dilution. Of these, 36 were positive on both arms. All except 8 were equal in diameter and had the same intensity of reaction. These varied from 1 to 5 mm. In 5 of these the ready diluted tuberculin produced the greatest diameter, while in 3 the freshly diluted had the advantage.

Of the 298 tests with the 1:100 dilution 64 were positive. Of these, all except 11 were equal in size on both arms and had the same intensity of reaction. These varied from 1 to 4 mm. In 7 there was a diameter of from 1 to 3 mm. greater with the ready diluted tuberculin and 4 were greater by from 1 to 4 mm. with the freshly diluted tuberculin.

Of the 116 tests done with the 1:10,000 dilution 30 were on previously recorded positive reactors (1918–1935). Of these, 20 reacted to the 1:10,000 on both arms, 3 were negative to the 1:10,000 but positive to the 1:100, 4 were positive to the 1:100, that being the only test used, while three were negative to both tests. None of these negatives had ever been found to have tuberculosis on X-ray examination. Thus the retest with ready diluted tuberculin showed gratifying agreement with the previous tests.

TESTS WITH THE READY DILUTED INCUBATED LOT 7H AND FRESHLY DILUTED LOT 7H

The next series of tests was conducted with the lot 7H ready diluted tuberculin, which had been in the incubator for 30 days at 37°C. and the freshly diluted as a control. Two hundred and thirty-five individuals were tested with the 1:10,000 dilution and 70 were found to be positive on both arms. One had a questionable reaction on the arm upon which the ready diluted incubated tuberculin had been given and a one-plus

on the control arm. In 19 of these, there was a difference in the size of the reactions, 13 in favor of the ready diluted incubated tuberculin and varying from 1 to 5 mm., in 6 the reactions were from 1 to 10 mm. greater with the freshly diluted tuberculin tests. With the 1:100 dilution 265 were tested and 44 were found to be positive reactors. Of these, all except 13 were equal in the size of reactions on both arms. In 8, reactions varying from 1 to 4 mm. were greater for the ready diluted tuberculin and in 5 from 1 to 5 mm. with the freshly diluted tuberculin. Although the sizes of the reactions were comparable the firmness of the induration varied. The incubated material tended to produce an appreciably softer induration, indicating some degree of deterioration in the tuberculin during 30 days incubation at 37°C. at 1:10,000 dilution.

Twenty-two of these tests were on previously reported positive reactors (1928–1934). All of these were positive either to the 1:10,000 or 1:100 dilutions.

TESTS WITH THE READY DILUTED LOT 21 AND FRESHLY DILUTED LOT 21

In the next series of tests using the ready diluted tuberculin and freshly diluted tuberculin, known as lot 21 (Michigan Department of Health), 207 tests were performed with the 1:10,000 dilutions. Of these, 56 were positive; 27 were equal in size and intensity; 26 varied from 1 to 5 mm. in favor of the ready diluted tuberculin, and 3 from 1 to 3 mm. in favor of the freshly diluted tuberculin. With the 1:100 dilutions 352 tests were performed, with 58 positive reactors. Of these, 44 had the same size of reactions, while 9 varied from 1 to 5 mm. in favor of the ready diluted tuberculin, while in 5 the reactions were from 1 to 3 mm. greater with the freshly diluted tuberculin. In this series only two tests were performed on previously reported positive reactors (1929-1936); both of these were positive.

ANALYSIS OF TESTS ON NEW ADMISSIONS

Upon further analysis it was found that completed tests were performed on 584 new patients. Of these, 164, or 28 per cent, were positive to the 1:10,000 dilutions. Upon X-ray examination 13 of these were found to have active childhood-type tuberculosis, 32 were inactive, 9 had adult-type tuberculosis, while 7 were considered suspects. Of the adult types 4 were minimal, 3 moderately advanced and one far advanced with unfavorable prognosis.

There were 420 negative to the 1:10,000 dilutions and retested with

the 1:100 of which 67, or 11.4 per cent of the 584 new patients, were positive reactors. Only one of these was diagnosed on X-ray examination as having an active childhood-type tuberculosis, 10 were inactive, while 2 had adult-type tuberculosis, one a minimal and the other moderately advanced.

On X-ray examination no tuberculosis was found in any of the non-reactors.

DISCUSSION

The diluent contained 0.5 per cent phenol. Although its use has been reported by other observers (12) it was thought possible that some of the patients might be sensitive to phenol. No study was made of reactions to 0.5 per cent phenol but the absence of false positive reactions shows that phenol sensitivity was not a complicating factor in our series. Long and Seibert (12) have recently reported that repeated tests of 0.5 per cent phenol in the diluent used with their Purified Protein Derivative showed no reactions. Phenol of this strength has been employed in many biologicals and so it was concluded that no harmful effects would be incurred with its use. On the other hand its ability to control bacterial decomposition far outweighs any disadvantage it might have.

Whether or not the diluent itself would sensitize sufficiently to cause false positives is an important question. The fact that there were no false positives in those receiving the second Mantoux test with the ready diluted tuberculin shows that the diluent itself did not sensitize the individuals in this study; at least they were not sensitized sufficiently to interfere with the usual sequence of Mantoux tests.

SUMMARY AND CONCLUSIONS

A total of 1,648 Mantoux tests were performed from December 15, 1936 to March 19, 1937, comparing tuberculin freshly diluted in saline with that ready diluted in the diluent of Gottschall and Bunney.

The results of these tests seem to indicate that the ready diluted tuberculin is as efficient as the freshly diluted tuberculin and retains its potency when kept at room temperature for a period of at least one month.

Tuberculin ready diluted 1:10,000 and incubated 30 days at 37°C. showed some deterioration evidenced by a difference in induration of the Mantoux reaction. Although the sizes of the reactions were comparable the induration was not quite as hard as that caused by freshly diluted material.

We wish to express our appreciation of the splendid cooperation we received from Dr. Arthur P. Derby, Director of Outpatient Department, Herman Kiefer Hospital, and Dr. Bruce H. Douglas, Tuberculosis Controller, Detroit Department of Health.

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RESULTS OF ARTIFICIAL PNEUMOTHORAX[1,2]

A Review of 530 Cases

GEORGE F. AYCOCK[3] AND PAUL E. KELLER[4]

We have felt that a statistical study of results obtained in cases of pulmonary tuberculosis under artificial pneumothorax is of value in determining the efficiency of this form of therapy only to the extent that such an analysis comprehends the varied pathological manifestations so treated. For instance, bare composite percentage results in a group of cases, ranging from recent localized exudative lesions to an extensive involvement, fibrocavernous in type, do not reflect the true potential of efficiency inherent in this therapeutic measure.

It is an attempt to overcome such a defect, in part at least, that this review undertakes the interpretation of results primarily on the basis of the dominant tissue reaction at the time artificial pneumothorax was induced in each case. In addition, the classification of the National Tuberculosis Association as to the extent of lesions has been applied.

We have felt that dominant tissue reactions can be embraced in three general groups, namely, exudative, caseous pneumonic and fibrocavernous. This is not intended as another classification of tuberculous lesions to be added to the confusing number now existing. The grouping in the manner described simply recognizes certain well known tissue reactions, which may be used as a basis for evaluating therapeutic indications and results. Probably it is in order that a brief description of each group be given.

Exudative group: It is realized that all lesions of reinfection have their inception as an exudative process. However, the use of this term may be permitted to describe tuberculous lesions in which the dominant tissue response at the moment is an exudative or inflammatory reaction. In general, such lesions show a tendency toward resolution, leaving relatively

[1] Read at a joint meeting of the Colorado Tuberculosis Association and the Denver Sanatorium Association, Denver, Colorado, February 18, 1938.

[2] From the Medical Service, Fitzsimons General Hospital, Denver, Colorado.

[3] Lieutenant Colonel, Medical Corps, U. S. Army.

[4] Captain, Medical Corps, U. S. Army.

little in the way of fibrous residuals, provided the issue is favorable. If cavities develop, they have soft, thin, yielding walls. In short, our description is of the group frequently designated as "soft" lesions. Pleural reactions occur with such lesions, but dense adhesions are not the rule.

Such a grouping may include lesions described under various classifications as benign exudative, exudative-productive, fibrocaseous-nodose and bronchopneumonic. We prefer to reserve the latter designation for lesions of lobular distribution, classified under the caseous pneumonic group, the nonresolving exudative group of Ornstein, Ulmar and Dittler (1).

The extent of the exudative reaction is believed to coincide in general with the size of the infection dosage. Regardless of extent, this reaction must be looked upon as a phase in tissue response to tuberculous infection (or reinfection). Sooner or later some sort of proliferative response occurs in all such lesions. In some cases the proliferative response may soon dominate the picture. In view of the foregoing it would seem more in keeping with the true order of tissue changes to describe such tuberculous lesions, not as exudative, but as in the exudative phase.

As previously stated, many lesions appear to clear up after their exudative phase, with slight residuals. Many others, however, do not. The necrotizing effect of heavy infection dosage, of which an extensive exudative reaction may be an index, is among the probabilities. The process, instead of resolving, may progress, and instead of residuals scarcely discernible there may be great areas of tissue destruction, replaced or circumscribed by fibrous tissue. This is the best defense under the circumstances, but a poor substitute for normal lung tissue.

Caseous pneumonic group: This group, in reality, has little to distinguish it from the exudative group, except for the intensity, and in some cases the extent of the tissue reaction. The separate grouping is largely a matter of clinical convenience.

According to Krause (2), conditions favoring the origin of such lesions are those which effect a high and sudden concentration of comparatively large numbers of tubercle bacilli within a tissue. The lesions may have a lobular or lobar distribution. In extreme cases an entire lung may be involved. The exudative reaction is intense. The high and sudden concentration of tubercle bacilli within a given area may result in rapid necrosis, giving rise to areas of excavation of irregular outline and poorly defined walls. In the cases of most extensive involvement, the disseminated lobular and the lobar distributions, there is likely to be intense

pleural reaction. Resolution is seldom more than partial in lesions of this type. In cases with a favorable issue the forces of repair come into play, as in the exudative group.

Fibrocavernous group: This group comprises cases in which the dominant tissue reaction at the moment is proliferative, an effort to repair or circumscribe tissue damage which has occurred during the exudative phase of the two groups previously described. While the dominant tissue reaction is proliferative, such cases may and often do show more recent lesions in an exudative phase.

Cases in this group show areas of cavitation, usually in the upper portions of the lungs, enclosed by fibrous walls of varying density and vascularity. As a result of fibrous retraction there is frequently some disturbance in the normal relations of the intrathoracic structures, such as a deviation of the trachea, displacement of the heart and mediastinum, etc. A fibrous pleurisy is usual and the incidence of pleural symphysis is high, especially over the areas of greatest tissue destruction.

Such lesions, regardless of clinical manifestations, constitute a menace, because they are potential chronic suppurative foci and as such give rise to degenerative visceral changes. In addition, they act as foci for future spreads of the tuberculous infection, as a result of haemorrhage or discharging infective material into the usual avenues of dissemination.

This review embraces 530 cases of artificial pneumothorax induced at Fitzsimons General Hospital. In 526 of these cases collapse therapy was begun in the year 1931, or thereafter. Four cases had their collapse therapy instituted and terminated in the preceding decade and chanced to come under our observation recently for other causes.

This series does not represent consecutive cases. On the other hand, it does not represent selected cases, but only those that had been followed up sufficiently to enable us to make an intelligent appraisal of the outcome or likely outcome.

In all cases definite intrapleural spaces were obtained as a result of artificial pneumothorax and many refills were given in each case in an effort to obtain a satisfactory collapse. Therefore, the term "unsatisfactory collapse" in no wise indicates that no intrapleural space was obtained. The term "satisfactory collapse," as used in the tabulations, denotes that the desired degree of collapse of the diseased area was obtained, with the closure of cavities, if present.

Sputum conversion, along with satisfactory collapse, has been made a

requisite for classifying treatment results as satisfactory in those cases still under collapse, or still in the process of reëxpansion. Completely reëxpanded cases have been listed under the terms "arrested" or "apparently cured," in accordance with the National Tuberculosis Association's usage of such terms. In short, our arrested cases have been free from symptoms, signs, etc. for a period of six months, at least, after completion of reëxpansion, while our apparently cured cases have shown such freedom for a period of two years, at least, after the accomplishment of reëxpansion.

Our statistical results are shown in tables 1 to 6, inclusive. Tables 1 to 4, inclusive, contain statistical data on artificial pneumothorax results alone, while tables 5 and 6 show the incidence of pleural exudate in the series of artificial pneumothorax cases. We chose to include special data on the incidence of this complication on account of its frequency and its importance in determining the future course of many cases.

RESULTS OF ARTIFICIAL PNEUMOTHORAX

It will be noted that table 1 shows composite results from the entire series of 530 cases. This table is self-explanatory and serves as a basis of comparison for tables covering the individual groups (tables 2, 3 and 4).

Exudative group: (table 2) The satisfactory results obtained in 100 per cent of the minimal cases may be taken only as a trend, as this series of 18 cases is too small to be used as a basis of opinion as to results to be expected in minimal cases generally.

The results in the moderately advanced cases were a surprise to us. While we were prepared for a good percentage of satisfactory results, 87.5 per cent was more than we expected. We rechecked our cases in this group to be certain no avoidable error had been made.

The results in the far advanced group were about as expected. The same may be said for the results in the exudative group generally, after making allowance for the high percentage of satisfactory results in the moderately advanced cases.

Results in this group, as well as in the other groups, confirm previous observations by many others to the effect that satisfactory results in artificial pneumothorax diminish in proportion to the extent of the treated lesion.

In our study of the cases comprising this group, the following features impressed us as important:

1: A large percentage of these cases, 73.5 per cent of the entire exudative group, showed satisfactory collapse. This was principally because of the nature of the lesions and the low incidence of dense pleural adhesions or symphyses encountered.

TABLE 1

Composite statistics for series—artificial pneumothorax

	SATISFACTORY RESULTS					UNSATISFACTORY RESULTS				
	Still under treatment; satisfactory collapse, sputum conversion	Re-expanded		Total cases, satisfactory results	Percentage satisfactory results	Unsatisfactory collapse but clinical improvement	Unsatisfactory collapse, no clinical improvement	Died	Total cases, unsatisfactory results	Percentage cases, unsatisfactory results
		Arrested	Apparently cured							
Minimal	5	11	2	18	100	0	0	0	0	0
Moderately advanced	50	40	24	114	86	18	1	0	19	14
Far advanced	88	50	31	169	44.5	91	77	42	210	55.5
Totals for series	143	101	57	301	57	109	78	42	229	43

TABLE 2

Exudative group—artificial pneumothorax

	SATISFACTORY RESULTS					UNSATISFACTORY RESULTS				
	Still under treatment; satisfactory collapse, sputum conversion	Re-expanded		Total cases, satisfactory results	Percentage satisfactory results	Unsatisfactory collapse but clinical improvement	Unsatisfactory collapse, no clinical improvement	Died	Total cases, unsatisfactory results	Percentage cases, unsatisfactory results
		Arrested	Apparently cured							
Minimal	5	11	2	18	100	0	0	0	0	0
Moderately advanced	50	39	23	112	87.5	15	1	0	16	12.5
Far advanced	58	38	24	120	62	52	14	7	73	38
Totals for group	113	88	49	250	73.5	67	15	7	89	26.5

2: The very nature of the process (tendency for lesions to be localized) in most of the minimal and moderately advanced cases, and some of the far advanced cases, favored the production of a "selective collapse." The advantages of this form of collapse will be described presently.

3: The healing process was rapid in a large percentage of cases. Apparent resolution was usually a quick accompaniment of satisfactory collapse.

4: The incidence of superimposed spontaneous pneumothorax was low. Only 12 cases, 3.5 per cent, were recorded in the whole group and these were confined to the rapidly progressive far advanced cases. Tuberculous empyema developed in seven of these cases. It might be mentioned that the only cases of superimposed spontaneous pneumothorax recorded in this and other groups were those causing symptoms. Many cases of small, superimposed, spontaneous pneumothorax, discovered on routine fluoroscopy, were asymptomatic.

Caseous pneumonic group: (table 3) This group includes only 25 cases and the percentage of satisfactory results is quite small, 28 per cent. The efficiency of artificial pneumothorax was modified chiefly by such factors as the extent of the lesions and the intensity of the pleural

TABLE 3

Caseous pneumonic group—artificial pneumothorax

	SATISFACTORY RESULTS					UNSATISFACTORY RESULTS				
	Still under treatment; satisfactory collapse, sputum conversion	Re-expanded		Total cases, satisfactory results	Percentage satisfactory results	Unsatisfactory collapse but clinical improvement	Unsatisfactory collapse, no clinical improvement	Died	Total cases, unsatisfactory results	Percentage unsatisfactory results
		Arrested	Apparently cured							
Moderately advanced...	0	0	1	1	100	0	0	0	0	0
Far advanced.....	0	4	2	6	25	5	*	13	18	75
Totals for group.....	0	4	3	7	28	5	0	13	18	72

* 13 such cases died.

reaction. The cases yielding satisfactory results were those showing localized bronchopneumonic or small lobar lesions. The cases with extensive lobar or disseminated lobular distribution showed unsatisfactory results. Owing to the intense pleural reaction in many of these cases, pleural symphyses were formed early, thus precluding the possibility of a free pleural space. In some cases where a free pleural space was found to exist, massive pleural exudate was formed on account of the intense pleural reaction already existing.

Superimposed spontaneous pneumothorax occurred in 7 cases. This accident was repeated in 3 cases. Contrary to what might be expected, only one such case developed sufficient pleural exudate to interfere with the continuance of artificial pneumothorax.

From the very nature of caseous pneumonic lesions, the tissues are in a highly sensitized state. In addition, there is a concentration of toxic products resulting from the high concentration of tubercle bacilli within a relatively circumscribed area of lung tissue. It is known that one of the first effects of collapse of the lung is the increased absorption of these toxic products. This amounts to what may be considered as an auto-tuberculinization, in the presence of tissues already highly sensitized, often with disastrous results. If artificial pneumothorax is to be given in such cases, collapse should be gradual, accomplished by small fills at frequent intervals.

Fibrocavernous group: (table 4) As might be expected, most cases in this group were far advanced. The percentage of cases showing sat-

TABLE 4

Fibrocavernous group—artificial pneumothorax

	SATISFACTORY RESULTS					UNSATISFACTORY RESULTS				
	Still under treatment; satisfactory collapse, sputum conversion	Re-expanded		Total cases, satisfactory results	Percentage satisfactory results	Unsatisfactory collapse but clinical improvement	Unsatisfactory collapse, no clinical improvement	Died	Total cases, unsatisfactory results	Percentage unsatisfactory results
		Arrested	Apparently cured							
Moderately advanced...	0	1	0	1	25	3	0	0	3	75
Far advanced.....	30	8	5	43	26.5	34	63	22	119	73.5
Totals for group.....	30	9	5	44	26.5	37	63	22	122	73.5

isfactory results is small, 26.5 per cent. The principal reason, of course, for the small percentage of satisfactory results is the large percentage of cases which showed unsatisfactory collapse. The large number of cases of unsatisfactory collapse resulted from mechanical barriers which were created by the forces of repair. The most important of these mechanical barriers were pleural adhesions and thick-walled cavities.

Pleural adhesions were encountered in all forms from small fiddle-string strands to extensive symphyses over the greater portion of a lobe containing a cavity. As a result of such adhesions, collapse in many instances was confined principally to that portion of the lung showing the least involvement. Such a collapse not only fails to accomplish its purpose, but interferes with the function of the healthy portion of the treated lung.

Thick-walled cavities, unyielding on account of the heavy fibrous constituency of their walls and adjacent lung tissue, were noted in most of the cases of unsatisfactory collapse. Such cavity walls and surrounding tissue frequently possess poor vascularity and even though collapse at times may be obtained the healing process is slow and uncertain.

Superimposed spontaneous pneumothorax occurred in 15 cases. This is an incidence of 9 per cent for the group. Tuberculous empyema occurred in 12 of these cases.

Marked thickening of the pulmonary pleura was of frequent occurrence in cases of this group under artificial pneumothorax. This may be accounted for, in part at least, by the longer periods of collapse required in these cases, repeated waves of pleural exudate and the fact that in this type the pulmonary pleura is frequently thickened before collapse is begun. Whatever its cause, we consider its presence of unfavorable augury, for, as a result of its development, there is a tendency toward fixation of the lung and its ability to reëxpand completely in the future becomes a matter of doubt.

Cases which showed considerable tissue destruction, but finally obtained satisfactory collapse, required auxiliary treatment in the form of phrenic nerve interruption. This procedure, by diminishing the capacity of the hemithorax, enables the treated lung, which has been made smaller by fibrous tissue replacement, to fill the hemithorax more completely. Thus, intrathoracic deformity, as a result of fibrous retraction, is minimized.

THE INCIDENCE OF PLEURAL EXUDATE

Table 5 shows composite statistics for the entire series on the incidence of pleural exudate, while table 6 gives such statistical data for each group. We have found that cases are rare indeed which do not show a small quantity of pleural exudate in the costophrenic angle at some time during the course of their artificial pneumothorax therapy. It is our custom to classify a case as having pleural exudate only if the level of the exudate is above the highest point of the hemidiaphragm on that side. Of course this is only an arbitrary determining point, as many cases may have this quantity of fluid and the occurrence be of no clinical significance.

The term "serous" exudate is self-explanatory. We have used the term "purulent" to describe the cloudy or thick exudates, whether incident to pure tuberculous empyema or the mixed infection type.

It will be noted from both tables 5 and 6 that in general the incidence of pleural exudate increases with the extent of the tuberculous process treated. For instance, the composite statistics (table 5) reveal that out of a total of 193 cases of pleural exudate 89 per cent occurred in far advanced cases. This is out of proportion to the percentage of far advanced cases under artificial pneumothorax in the entire series, 71 per cent.

By comparing group statistics, it will be noted that the incidence is

TABLE 5

Composite statistics for series—incidence of pleural exudate

	TYPE OF EXUDATE		CAUSE FOR ABANDONMENT OF THERAPY	PERCENTAGE OF CASES IN WHICH EXUDATE INTERFERED WITH THERAPY	PERCENTAGE OF CASES SHOWING PLEURAL EXUDATE
	Serous	Purulent			
Minimal	2	0	0	0	11
Moderately advanced	18	1	0	0	14
Far advanced	151	27	45	12	47
Totals for series	171	28	45	8	37.5

TABLE 6

Incidence of pleural exudate

	SEROUS	PURULENT	CAUSE FOR ABANDONMENT OF THERAPY	PERCENTAGE OF CASES IN WHICH EXUDATE INTERFERED WITH THERAPY	PERCENTAGE OF CASES SHOWING PLEURAL EXUDATE
Exudative group					
Minimal	2	0	0	0	11
Moderately advanced	17	0	0	0	13
Far advanced	74	7	12	6	42
Totals for group	93	7	12	3.5	29.5
Fibrocavernous group					
Moderately advanced	1	1	0	0	50
Far advanced	72	19	30	18.5	56
Totals for group	73	20	30	18	56
Caseous pneumonic group					
Far advanced	5	1	3	12	24

almost twice as high in the fibrocavernous group as in the exudative group, the percentage ratio being 56 to 29.5. The same comparative study shows that, of the cases in which pleural exudate interfered with the continuance of artificial pneumothorax, the percentage ratio was higher, 18 to 3.5. The incidence of purulent cases was higher in the fibrocavernous group; the percentage ratio was 12 to 2.

One of the most gratifying pieces of statistical information regarding the development of pleural exudate in this series of cases is the low incidence in the minimal and moderately advanced exudative cases. The incidence rates for these groups are 11 per cent and 13 per cent, respectively. Not a case of either group showed purulent exudate, nor was there a case in either group in which the development of pleural exudate caused the abandonment of artificial pneumothorax.

DEATHS

The deaths in all groups occurred in cases which had not obtained satisfactory collapse. All deaths were due to toxaemia and not immediately due to any of the accidents accompanying artificial pneumothorax. Undoubtedly, in some of the cases of superimposed spontaneous pneumothorax death was hastened by this accident. Air embolism was not a factor in any of the deaths.

MECHANISM OF HEALING IN CASES UNDER ARTIFICIAL PNEUMOTHORAX

Many theories have been advanced as to the mechanism of healing in tuberculosis and especially as to the action of artificial pneumothorax in this respect. The theories involving localized ischaemia, lymph stasis and localized rest are almost as old as the procedure itself. The more recent hypothesis of Coryllos (3) seeks to explain healing on the basis of lobar or lobular atelectasis, which in turn produces a tissue anoxaemia, a condition inimical to the growth and development of tubercle bacilli. All of these factors may play some part in the healing process, or perhaps we have not found the real answer as yet.

One feature relative to the healing of cavities has been impressed upon us in the review of this series of cases. In this respect we have noted that cavities are seldom collapsed in the mechanical sense immediately after induction of artificial pneumothorax. Their closure has appeared to us a gradual process resulting from the augmentation of natural healing forces by artificial pneumothorax. In further support of this opinion may be mentioned the fact that in the overwhelming majority of our

cases, particularly in the exudative group, collapse has been accomplished by hypotensive pneumothorax. Our refills were small, usually 300 cc. and less, repeated at frequent intervals. In our satisfactory cases, cavity closure was gradual but progressive under this method and we have failed to find record of a case in this series where departure from this method converted an unsatisfactory collapse into a satisfactory one.

REQUISITES OF AN EFFICIENT ARTIFICIAL PNEUMOTHORAX

Artificial pneumothorax, in our opinion, should be regarded essentially as a temporary therapeutic measure. In general, we feel its rating of efficiency can be measured in terms of its ability to accomplish desired clinical results while meeting the following conditions:

1: That as much normal lung tissue as possible be permitted to function while this result is being accomplished.
2: That upon completion of this therapeutic procedure (reëxpansion) the treated lung retain as much of its anatomical and functional integrity as conditions will permit.

Both of these conditions are met in the so called "selective collapse," which, as previously stated, has been applicable in a good percentage of cases in this series, notably in the exudative group. We agree with Ellison (4) in the statement that the development or production of this type of collapse is beyond the control of the operator. The selective feature of collapse obtains only as a result of the application of definite aerodynamic principles in the presence of certain manifestations of pathological anatomy and pathological physiology. Recent literature abounds in explanations of the mechanism of its production, too well known to recount for the purposes of this discussion. Suffice to state that the only act on the part of the operator which may predetermine the successful issue of this procedure is the proper selection of cases presenting the conditions favoring its production.

THE SELECTION OF CASES FOR ARTIFICIAL PNEUMOTHORAX

Our analyses of results obtained in the various groups show that by far the largest percentage of satisfactory results from artificial pneumothorax was obtained in the exudative group. It has been held by many that in this group there is a strong tendency toward spontaneous healing and that many cases will recover without collapse therapy. On this point there is no argument. The problem which confronts us lies in the

determination of those cases which may or may not terminate favorably under expectant treatment. The characteristic of exudative lesions which admits of little argument is that they do not remain stationary, as such, for any considerable period of time. These lesions usually establish a trend, either progressive or recessive, in a very short time, so that no protracted periods of observation should be necessary to determine this point. As an illustration, many of our patients at Fitzsimons General Hospital are soldiers sent from distant stations, including our overseas garrisons. Transfer clinical records and X-ray films accompany these patients. In most of the cases showing exudative lesions, we are able to determine their trend upon arrival at this hospital by comparing our findings, clinical and X-ray, with those noted at the home stations of these soldiers.

It would seem, therefore, that the statistical argument in favor of artificial pneumothorax becomes strong in all exudative cases which have failed to establish a favorable trend. The contrast in the percentage of satisfactory results between far advanced cases of the exudative and fibrocavernous groups (62 per cent and 26.5 per cent, respectively) leaves little to be said as to the choice of artificial pneumothorax as a therapeutic measure while the lesions are in the exudative phase. The percentage of satisfactory results in minimal and moderately advanced exudative cases should be even more convincing. In these groups, the highly satisfactory percentage results (100 per cent and 87.5 per cent, respectively) were obtained with inconsequential risk of untoward complications. Furthermore, the mere fact that a case may be classed as minimal or moderately advanced does not mean that it lacks the potentialities of a progressive lesion. It often transpires that the minimal or moderately advanced exudative case of today will be a far advanced fibrocavernous case a year hence. It would seem that such a patient who has been following a "watchful waiting" policy has paid dearly for the delay.

The relatively poor percentage results shown for the fibrocavernous group does not mean that such cases should not be given the benefit of an attempt at artificial pneumothorax. However, it should be borne in mind in initiating the therapy in cases of this group that the chances of satisfactory results are less and that if a satisfactory collapse is obtained it must of necessity be maintained for a longer period of time than in the exudative cases. In this connection, we are in accord with the opinion of Eglee and Jones (5) to the effect that in the exudative case the es-

sential purpose of artificial pneumothorax is to shift the immunobiological balance in favor of the patient, while in the fibrocavernous case it is mechanical, to correct a tissue defect (cavity) which constitutes a potential focus of future tuberculous spread.

REËXPANSION

From our observations in cases comprising this series we are convinced that the determining factor in initiating reëxpansion should be the condition of the treated lung, together with the general condition of the patient. The time element of collapse should be of secondary importance. Many exudative cases have shown sufficient evidence of healing in the treated lung to permit the initiation of reëxpansion after twelve months of collapse. We feel that reëxpansion should be a gradual process with frequent fluoroscopic observations and roentgenograms. Since the diseased portion of the lung is last to reëxpand, a definite opinion as to the condition of this portion of the lung can be formed before all the intrapleural air space is lost. In the exudative group of our series, 21 of the moderately advanced and far advanced cases, classed as apparently cured, were collapsed for periods ranging from sixteen to twenty-five months. They have been reëxpanded for periods ranging from two to thirteen years, and, as their classification indicates, no reactivation has been noted. In fibrocavernous cases periods of collapse unquestionably should be longer.

We have felt that many cases, particularly of the exudative group, have remained collapsed too long. Periods of prolonged collapse, aside from inconvenience to the patient, promote thickening of the pulmonary pleura, with a consequent tendency toward fixation of the lung, and increased fibrosis in the treated lung, associated with the development of such conditions as chronic bronchitis, bronchiectasis, emphysema and bronchial stenosis. Thus the patient is converted into a state of chronic partial invalidism.

There seems to be a general fear of reëxpansion because of the danger of "opening up" healed lesions. It is not apparent to us why a healed lesion in a reëxpanded lung should reactivate any more readily than a healed lesion in a lung which has never had artificial pneumothorax. It has been our opinion for a long time that lesions which "open up" as a result of the so called added strain incident to reëxpansion are not healed lesions in the first place.

Unquestionably some of our reëxpanded cases will show reactivation.

So will many cases which have shown apparent healing without artificial pneumothorax. The mere act of keeping the lung collapsed for a longer period of time is not going to be a guarantee against such occurrences. While it is believed that artificial pneumothorax limits spreads in most of the recent cases obtaining a satisfactory collapse, it does not follow that a spread cannot occur in a collapsed lung. We have had the unpleasant experience of seeing several of our cases develop spreads in the collapsed lung where we thought the collapse was satisfactory.

SUMMARY

1. A total of 530 cases of artificial pneumothorax have been reviewed.

2. Analyses of results were based essentially upon dominant tissue reactions at the time artificial pneumothorax was induced in each case. These dominant tissue reactions were considered under three general groups, exudative, caseous pneumonic and fibrocavernous. The classification of the National Tuberculosis Association, as to extent of lesions, was applied in each group analysis.

3. Satisfactory results were obtained in 301 cases, or 57 per cent, of the entire series. In the exudative group alone, the percentage of satisfactory results was 73.5. In the total of 301 cases obtaining satisfactory results, there were 250 cases of the exudative group, or 83 per cent. The incidence of important complications, such as pleural exudate and superimposed spontaneous pneumothorax, was highest in the fibrocavernous group.

4. The grouping as described does not represent special types of tissue reactions, but is intended to comprehend the phases of essential tissue reactions to tubercle bacilli. For instance, lesions in the exudative group, in reality, are in the exudative phase, which is more or less transitory. The high percentage of satisfactory results from artificial pneumothorax in cases of this group simply means that this is the optimum phase in which to apply this form of therapy. In this phase, the mechanical barriers, resulting from the fibrosis incident to healing and tissue replacement, have not become dominant. Accordingly, satisfactory collapse is obtained more readily. On the other hand, the fibrocavernous group comprises cases in the healing or reparative phase. Fibrosis has become the dominant tissue reaction and as a result certain mechanical barriers have been formed, which threaten the successful issue of artificial pneumothorax. The caseous pneumonic group represents cases in a sort of intensified exudative phase. The number of

such cases reviewed is too small to serve as a basis for definite conclusions as to the results of collapse therapy.

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LOBECTOMY AND THORACOPLASTY IN THE SAME PATIENT

A Report of Three Cases[1]

RICHARD H. OVERHOLT AND REEVE H. BETTS

The coexistence of more than one chronic disease in the same individual is often considered as a contraindication in itself to major surgical treatment of either condition. In the past, such an attitude has prevailed in regard to the treatment of patients who have both pulmonary tuberculosis and bronchiectasis. Either one of these disease entities, if existing alone, may require surgical therapy if an arrest or cure of the disease is to be expected, and such treatment is rapidly becoming standardized; selective thoracoplasty for pulmonary tuberculosis, and lobectomy for bronchiectasis. Evidently there has been a definite reluctance to recommend the use of both procedures in the same patient, as a search of the literature has revealed only one reference, that made by Alexander (1) of a case successfully operated by Eloesser.

Four years ago, we performed lobectomy in a patient with arrested tuberculosis who had been having repeated haemorrhages from an atelectatic lower pulmonary lobe. Subsequently, tuberculosis of the upper lobe became active, the control of which required an upper selective thoracoplasty. Within the past year, two other patients have been treated by a combination of these two operations. In the second and third patients, however, thoracoplasty preceded lobectomy. In both of these patients satisfactory selective thoracoplasty and upper lobe mobilization were obtained, cavities in the upper lobe were closed, and the sputum was converted. Persistent cough and copious expectoration led to bronchographic studies. Lower lobe bronchiectasis was demonstrated and was either coincidental to, or was a sequela of, the upper lobe tuberculosis. Lobectomy was successfully carried out in

[1]A fourth case has been operated very recently. A right lobectomy (lower and middle lobes) was done for bronchiectasis fifteen months ago. At that time no evidence of active pulmonary tuberculosis was found although there was evidence of a healed process in the extreme right apex. One year after lobectomy, a 3 cm. cavity appeared in the right upper lobe and the sputum was found to be positive. A right upper thoracoplasty was successfully carried out.

both patients. The bronchial fistulae closed spontaneously, and wound healing was not delayed. In all three patients the tuberculosis has been arrested, and the effects of bronchiectasis have been relieved. This experience indicates that the coexistence of the two diseases in the same individual does not necessarily contraindicate surgical treatment of either or both.

Case Reports

Case 1: L. W., white, single, female, age thirty-five. Tuberculosis of the left lung was discovered when the patient was twenty-one years of age. There was a history of haemoptysis, fever, positive sputum, and at that time the patient was admitted to the Westfield State Sanatorium. An attempt to induce pneumothorax failed. After thirteen months' hospitalization, the patient returned home where bed-rest was continued for ten months. In 1919 she resumed her work as a stenographer and continued working for a period of ten years. During this interval the patient was in good health except for a short period when pneumonia followed an appendectomy. In 1930, pain in the left chest, cough, haemoptysis and weight loss forced the patient to stop work. After two years' bed-rest at home, she entered the Bristol County Hospital, Attleboro, Massachusetts. Upon examination at that time percussion over the left lower chest revealed dulness. A friction rub could be heard at the left base posteriorly. Crepitant râles were heard below the clavicle on the same side. The sputum was positive during the first three months of her sanatorium residency, but was consistently negative after that time.

A left temporary phrenic paralysis was done April 15, 1933. A diminution of the pain in the chest was noted for a period of two months. Cough, expectoration and occasional haemoptysis continued. Bronchography demonstrated atelectasis and bronchiectasis of the left lower lobe (figure 1A). On April 22, 1934, a left lower lobectomy was carried out by the tourniquet method under intratracheal cyclopropane anaesthesia. The chest was drained by a single catheter. The convalescence was uneventful. A bronchial fistula developed, but closed spontaneously, and the drainage tube had been removed and the wound completely healed by the time of discharge, thirty days after operation. All symptoms disappeared for a period of two months following lobectomy. Then, cough and expectoration of positive sputum reappeared. Crepitant râles could be heard in the subclavicular area on the left. The roentgenogram showed increased density of the left lung field, but a definite area of cavitation could not be demonstrated. Left upper thoracoplasty with removal of segments of the upper seven ribs was carried out in three stages between May and September, 1935. A disappearance of symptoms followed and the sputa have been consistently negative upon examination

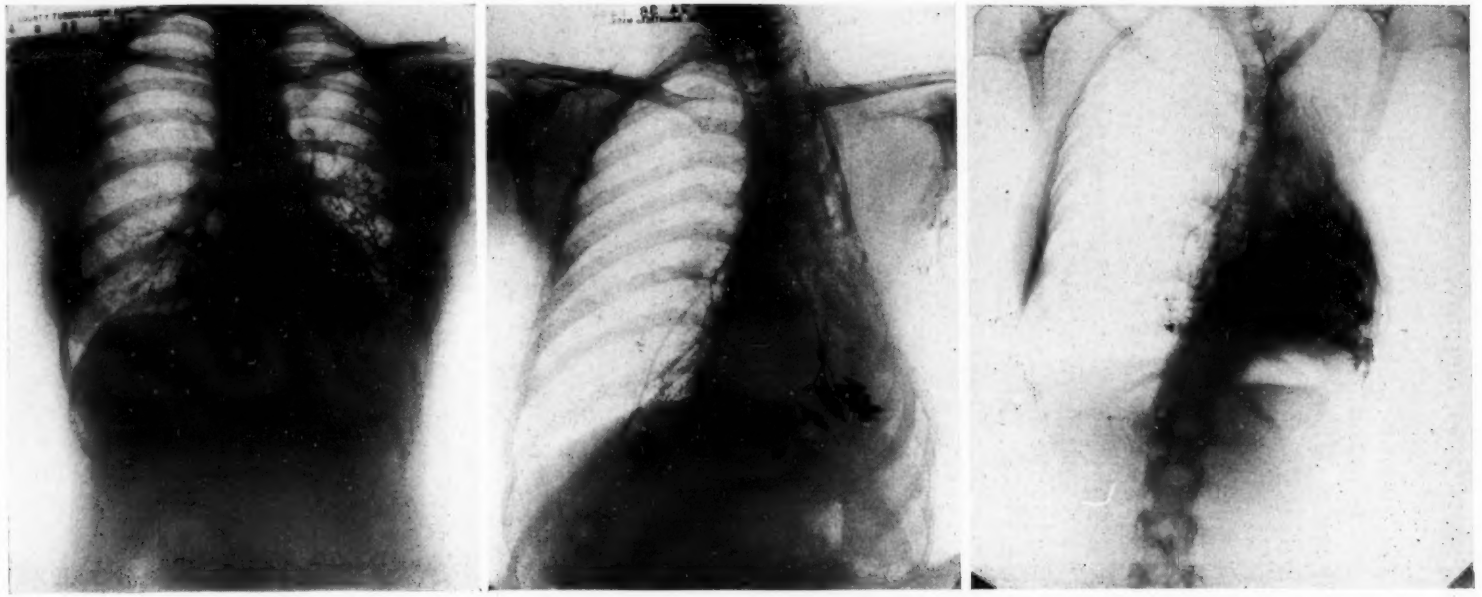

FIG. 1A FIG. 1B FIG. 1C

FIG. 1. Bronchograms (retouched) demonstrating bronchiectasis of the left lower lobe in the three reported cases. (A) Case 1 before lobectomy and thoracoplasty. (B) and (C) Cases 2 and 3 preceding lobectomy, but following left upper thoracoplasty for tuberculosis.

after concentration. The patient was discharged from the sanatorium seventeen months after thoracoplasty. During the past year she has been employed as a full time secretary and has been leading a normal life (figure 2A).

Case 2: H. H., a thirty-two year old salesman, was admitted to the Norfolk County Sanatorium April 11, 1932, because of cough and hoarseness of four months' duration. Physical and roentgenological examination disclosed moderately advanced, cavernous tuberculosis, involving the left upper lobe. The average amount of sputum each twenty-four hour period was thirty grams,

FIG. 2A

FIG. 2B

FIG. 2C

FIG. 2. Photographs of patients following selective left upper thoracoplasty for pulmonary tuberculosis and left lower lobectomy for bronchiectasis. Note general state of nutrition and lack of deformity. Two patients have been rehabilitated, and the third is greatly improved. (A) Case 1. (B) Case 2. (C) Case 3.

and tubercle bacilli were found. Pneumothorax gave unsatisfactory collapse and was discontinued. A three-stage thoracoplasty was carried out between November, 1933 and July, 1934, segments of the upper seven ribs on the left side being removed. His general condition improved, his sputum became negative, and the patient was discharged as arrested in June, 1935. Two months later, he contracted an upper respiratory infection. Cough and profuse expectoration followed. Upon his readmission to the sanatorium the daily amount of sputum was recorded as 720 gm. Moderate dyspnoea and anorexia were present. His weight decreased from 154 to 128 pounds.

Roentgenological examination of the chest following instillation of lipiodol showed marked saccular bronchiectasis of the left lower lobe and of the lingula of the left upper lobe (figure 1B). Bronchoscopic examination disclosed stenosis of the left lower lobe bronchus. Bronchoscopic dilatation of the stenosed area was done on four occasions between April, 1936 and February 1937, resulting each time in a brief period of symptomatic improvement. Lobectomy was done on February 6, 1937, under intratracheal cyclopropane anaesthesia. An incision was made in the lower portion of the thoracoplasty scar and an adequate exposure obtained by removal of a liberal portion of the eighth rib, a short posterior segment of the ninth rib, and fragments of regenerated ribs above. The lower lobe was removed by the tourniquet method. The lobe was adherent throughout, but mobilization of the lobe was accomplished without difficulty due to the thin, filmy, avascular character of the adhesions. The fissure between the upper and lower lobes was well developed. The lower anterior bronchus of the upper lobe was isolated, divided and the lingula of that lobe was removed. A catheter was placed in the chest through a stab wound. Postoperatively the course was satisfactory. The wound healed by first intention. A bronchial fistula, which developed on the seventh postoperative day, closed without difficulty. The patient returned to the sanatorium twenty-two days after operation. The sputum has now decreased to less than one ounce in twenty-four hours. The general condition of the patient is much improved (figure 2A), and dyspnoea is less marked.

Case 3: L. C., a twenty year old, single, white female, was admitted to the Essex County Sanatorium in April, 1934, complaining of fatigue, cough and weight loss of fifteen months' duration. Examination at that time revealed bilateral pulmonary tuberculosis with a cavity 7 cm. in diameter in the left upper lobe. The patient was extremely toxic carrying a sustained temperature of 100° to 101°F. Pneumothorax failed to provide adequate collapse and was discontinued. The patient continued to do badly, the fever continued, and weight loss was progressive. The left phrenic nerve was crushed in October, 1934. The temperature gradually subsided and her general condition improved during the following fifteen months. A seven-rib left upper thoracoplasty was carried out in January and March of 1936, this procedure being carried out in two stages. The cavity closed and the sputum was converted, but the amount of sputum was not materially reduced, and remained at 160 to 180 gm. Bronchography disclosed atelectasis and marked bronchiectasis of the left lower lobe; also minimal bronchiectasis of the right lower lobe (figure 1C).

On February 25, 1937 a resection of the left lower lobe was carried out under intratracheal cyclopropane anaesthesia. The lower part of the thoracoplasty scar was reopened and the interior of the chest exposed after resection of the

eighth rib and short posterior segments of the seventh and ninth ribs. Mobilization of the lower lobe was accomplished without difficulty. The hilum was divided after a tourniquet was applied. Two catheters were placed in the chest for drainage. The postoperative course was satisfactory and the wound healed by first intention. A bronchial fistula developed on the eleventh postoperative day, but closed twelve days later, and the patient was transferred to the sanatorium twenty-six days after operation.

Her general condition has been greatly improved (figure 2C). The existing disease in the contralateral lower lobe is sufficient to explain a persistent slight cough and expectoration of 30 to 40 gm daily. The patient has been discharged from the sanatorium and remains in relatively good health.

SUMMARY

Three patients are reported in whom upper thoracoplasty for a tuberculous process in the upper lobe and lobectomy for bronchiectatic disease of the lower lobe were advised in the same patient. The operation was successfully carried out in all three patients. In each individual the tuberculosis was arrested at the time of lobectomy. No technical difficulty was encountered in the mobilization of the lobes. The thoracic wounds healed by first intention. Closure of the bronchial fistula in each instance was not prolonged.

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HEALING OF EXPERIMENTAL PULMONARY TUBERCULOSIS BY FASCIAL TRANSPLANTATION AND BRONCHIAL LIGATION[1, 2]

LUCILO ESCUDERO AND W. E. ADAMS

The treatment of cavernous pulmonary tuberculosis by collapse therapy has made rapid advances during the last decade. With the development of the technique for thoracoplastic collapse of the lung, many patients with large pulmonary cavities, who otherwise would have had no chance for recovery, have been completely cured. Previous to this recent advance, the use of pneumothoracic collapse of the lung had led to the cure of a still larger number of patients. Unfortunately, however, physical and biological conditions not infrequently prevented the production of a satisfactory collapse of tuberculous lesions. The fact that several surgical procedures other than thoracoplasty have been devised and utilized with a variable degree of success, testifies that thoracoplastic and pneumothoracic collapse therapy are not infrequently either contraindicated or inadequate. Eloesser (1) has recently clearly demonstrated the futility of attempts to collapse certain "circular cavities" by the above named procedures. Cavities with a check-valve communication with the bronchial tree, which permits free entrance but difficult escape of air, tend to move over to the mediastinum with pneumothoracic collapse or with collapse of the thoracic wall. They also tend to form "hanging cavities" when adhesions, too large to divide, prevent a pneumothorax from producing a satisfactory collapse.

In a recent communication two methods of producing collapse of the lung in experimental animals were described (4). A method has been devised (2, 3) for the production of tuberculous cavities of the lung in dogs similar to those seen in clinical cases. The purpose of this experimental investigation was to determine the effect of the two methods of collapse upon cavernous pulmonary tuberculosis produced experimentally in dogs.

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[2] This work was done under a grant from the Douglas Smith Foundation of the University of Chicago.

EXPERIMENTAL METHODS

The tuberculous lesions were produced in the following manner. Under morphine anaesthesia and fluoroscopic control a bronchoscope was passed. A ureteral catheter was then introduced into the finer ramifications of an air passage and 0.2 cc. of a heavy suspension of human tubercle bacilli in lipiodol deposited. The course of the lesion produced was closely followed by fluoroscopy and roentgenography. Cavities from 1.5 to 3.5 cm. in diameter were routinely produced and were demonstrable on X-ray examination.

The massive bronchogenic infection with tubercle bacilli, followed by caseation and elimination of the necrotic material through the bronchi, led to the formation in the lung of excavations, or rather tuberculous abscesses which were separated from the pulmonary parenchyma by a membrane of variable thickness. Where their caseous content had been emptied through the bronchi they represented "holes" in the lung which communicated with the bronchial tree through one or more draining bronchi. It is not the purpose of this presentation to go into great detail concerning the mechanism of the production of cavities. However, it is quite likely, due to the elasticity of the lung structure, that the destruction of a very small amount of pulmonary parenchyma may lead to the development of a cavity several times larger than the amount of tissue destroyed.

The regularity of production of tuberculous lesions by this method is of great importance. This being true, the effect of collapse therapy on these lesions could be extremely well controlled and evaluated. The following methods of pulmonary collapse were used in the treatment of these cavernous lesions.

FASCIAL COLLAPSE

After a preliminary injection of morphine each dog was prepared for a sterile operation. A fascial transplant was obtained, first from the leg, and later in order to have more material, from the abdominal wall (rectus sheath). Under positive pressure intratracheal ether anaesthesia, the pleural cavity was opened by an eight centimetre incision in the fifth intercostal space. The selected lobe was brought out and its volume reduced by spontaneous relaxation by decreasing the positive pressure. The fascial transplant was then sewed snugly around it so as to cover its entire surface. The envelopment was begun at the hilum and proceeded toward the periphery using interrupted sutures. Care

was necessary not to constrict the vessels at the hilum. The intratracheal pressure was increased, the other lobes reinflated to exclude the pneumothorax and the chest wound closed.

BRONCHIAL LIGATION

Ether was administered by the intratracheal insufflation method at a pressure of from 20 to 30 mm. of mercury. The chest was opened through an incision in the fifth intercostal space. The lung was reflected anteriorly and the primary or stem bronchus was isolated from the surrounding tissues. A double ligature of linen was passed around the bronchus, care being taken to avoid including the bronchial arteries and nerves in the ligatures. The central ligature was tied and before the distal ligature was approximated 0.05 to 0.1 cc. of a 10 to 35 per cent solution of silver nitrate was injected into the bronchus between the two ligatures. In other animals both ligatures were tied before the injection of 0.05 cc. of a 10 per cent solution of silver nitrate was made. In some cases the insufflation was interrupted for a few seconds to allow collapse of the lung, and after its collapse, the ligature was firmly tied. The insufflation was again started, and the total occlusion of the brochus tested by attempts to distend the lung. The chest was then closed with pericostal sutures, the remaining pulmonary tissue being distended with air before the last suture was tied to obviate a large postoperative pneumothorax. This operation required only a few minutes for its performance, and was carried out in each case without mishap. The postoperative course was studied by frequent fluoroscopic and roentgenographic observations. Massive atelectasis of the obstructed lobe developed and the mediastinum and diaphragm were displaced toward the collapsed lobe. No exudate was seen in the pleural cavities. Bronchoscopic examinations were made and bronchial occlusion verified.

EXPERIMENTS

Fascial transplantation: Ten dogs were used and were divided into two groups. In the first group (A) of six dogs, the lesions were produced bilaterally with the subsequent collapse of one side, the other side remaining as a control. In the second group (B) of four dogs a tuberculous lesion was produced in a single lobe, the right middle, this being collapsed subsequently by a fascial transplant.

Group A: Following operation the animals appeared sick; progressive destruction of the uncollapsed control cavity was observed; and in two

dogs a tuberculous empyema developed with death of the animals. One dog died of distemper four days after the operation; one died of gangrene of the lung two days after operation; and two were sacrificed three months after operation. Only one dog died as a direct result of this operation. This was due to constriction of the vascular supply of the pulmonary lobe by the fascial transplant at the hilum. When care was exercised later this complication was obviated. All collapsed lobes showed progressive healing of the tuberculous lesion whereas the non-collapsed lesion became more advanced and developed pleural exudate in two cases.

Group B: One of the four dogs in the unilateral group died of a pre-existing distemper five days after operation; one died of postoperative massive atelectasis of the unoperated lung two days after operation. Two dogs were healthy when sacrificed at two and three months after the operation. In all lobes where the tuberculous cavities were collapsed by fascial transplant, progressive healing of the lesion was noted and no pleural exudate developed.

Comment: In order to study the reaction to operation of acute and subacute lesions, surgical collapse was produced at intervals from a week to three months after infection. Both acute and chronic lesions responded favorably to the treatment and the results of operation were very satisfactory.

In one case, although it was necessary to divide extensive adhesions produced by a cavity near the pleural surface, there was little or no pleural effusion following the application of the fascial transplant.

The operation was facilitated by allowing spontaneous relaxation of the affected lobe by a short interruption of the positive intratracheal pressure. After losing an animal from acute massive collapse of the other lung, we attempted to prevent bronchial dissemination of the contents of the cavities by temporary compression of the bronchus of the tuberculous lobe with a soft clamp. In spite of rather marked manipulation of such a lobe during some operations, we never observed the complication again.

The single dog which developed a pleural effusion on the operative side had contracted distemper prior to the operation. An excessive compression of the lobe with fascia was found to be dangerous (763, table 1) and if the amount of fascia is not sufficient the compression should be limited to the area containing the cavity. The best results were obtained by the use of a large enough piece of fascia to enable the

maintainance of the lung in a position of spontaneous relaxation, thus avoiding dangerous compression. The operation was always well tolerated, the free transplant always "took" and there developed no pleural effusion. Few adhesions were found within four to six days after operation, but they were usually quite extensive in dogs sacrificed after three months. These adhesions, however, did not interfere with centripetal retraction of the enclosed lobe nor with the occlusion of cavities. Roentgenograms reveal a progressive diminution of the volume of the enclosed lobes (figures 1 and 4). X-ray films of the speci-

TABLE 1

Treatment of pulmonary tuberculosis by fascial transplantation

DOG NUMBER	INFECTED BEFORE OPERATION	DURATION OF COLLAPSE	RESULTS
	days		
763 B	5	2 days	Died of gangrene.
786 B	21	4 days	Died of previous distemper.
787 B	1	3 months	Died of exudate from other lobe; operated lobe, good collapse, cavity closed. Healing.
771 B	17	19 days	Died of exudate other side. Operated lobe, good collapse. No cavity. Healing lesion.
762 B	31	3 months	Sacrificed. Good collapse. Healing. No cavity.
784 B	9	3½ months	Sacrificed. Good collapse. Healing. No cavity.
878 U	28	5 days	Died of previous distemper. Operative lobe, good collapse.
880 U	7	2 days	Died of massive lung collapse other side. Operative lobe, good collapse.
858 U	27	3 months	Sacrificed. Good collapse. Healing. No cavity.
966 U	26	2 months	Sacrificed. Good collapse. Healing. No cavity.

B—Bilateral.
U—Unilateral.

mens revealed no obstruction of the primary bronchi. Thus the mechanism of this form of collapse therapy is entirely different from the second method employed.

Many of the experimental cavities had attained considerable size before the fascial transplant was performed. After operation, however, they rapidly regressed as demonstrated by frequent roentgen-ray visualizations, and, at autopsy three months later, only fibrous tissue scars remained at the site of the previous cavity with only cellular reaction remaining. The cavities in the inflated, control lobes, however, continued to increase in size and were always present at autopsy. These

FIG. 1A

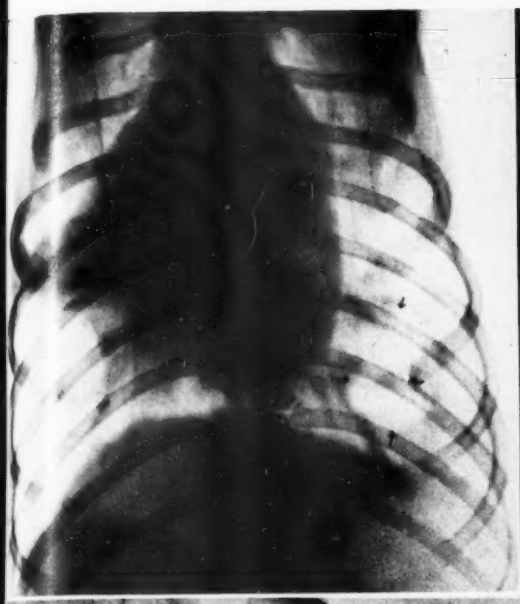


FIG. 1B

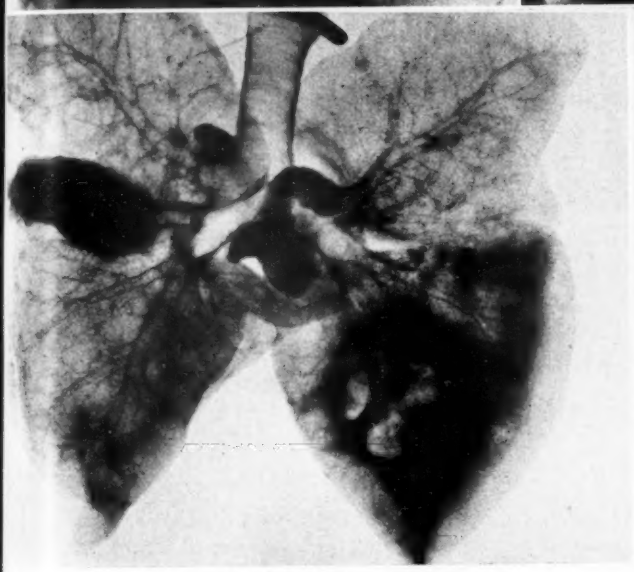


FIG. 1C

FIG. 1D

FIG. 1A. Anteroposterior X-ray of chest of dog 762. Note fascial collapse on the right side, and a huge, irregular shaped cavity on the left side. (3.5 months after infection and 2.5 months after collapse.)

FIG. 1B. Lateral view of same dog.

FIG. 1C. X-ray of specimen of the same dog showing no obstruction of the primary bronchi collapsed by fascia. The cavity in the left side reveals some of the characteristics of these lesions.

FIG. 1D. Photograph of specimen of dog 762, revealing the right collapsed lobe cut open and healing of the tuberculous cavity. On the left side the control lesion, which consumes a large part of the lobe, is seen.

results indicate that fascial transplant collapse of the lung was efficient in closing and healing the experimentally produced tuberculous cavities (figure 1).

Bronchial ligation: The second method of producing collapse of the lung, namely bronchial ligation, was used in the treatment of cavernous pulmonary tuberculosis in a series of 12 dogs.

TABLE 2

Treatment of pulmonary tuberculosis by bronchial ligatures

DOG NUMBER	INFECTED BEFORE OPERATION	DURATION OF COLLAPSE	RESULTS
477 B	21 days		Died of anaesthesia during operation.
393 B	2 months	13 days	Died of silver nitrate necrosis. Lobe atelectatic. Lesion improved.
434 U	21 days	4 days	Died of previous distemper. Bronchus occluded.
400 U	35 days	7 days	Died of silver nitrate necrosis. Pneumonia.
15 U	22 days	3 months	Incomplete occlusion. Bronchiectasis. Cavity present.
14 U	2 months	2 months	Sacrificed. Bronchus occluded. Atelectatic. Healing. No cavity.
959 U	1 month	4.5 months	Sacrificed. Bronchus occluded. No cavity. Scar.
584 U	2.5 months	7 days	Died of intestinal obstruction. Bronchus occluded. Atelectatic.
594 U	6 weeks	4.5 months	Sacrificed. Bronchus occluded. No cavity. Healing scar.
687 U	6 weeks	4.5 months	Sacrificed. Bronchus occluded. No cavity. Healing scar.
689 U	2.5 months	3.5 months	Sacrificed. Bronchus occluded. No cavity. Scar, 0.4 cm. diameter.
861 U	3 months	3 months	Sacrificed. Bronchus occluded. No cavity Small healing scar.

B—Bilateral.
U—Unilateral.

Until a few years ago it had been believed that bronchial obstruction with resultant atelectasis was an unfavorable complication of pulmonary tuberculosis. Good results had been reported following the treatment of this complication by artificial pneumothorax. In some cases of this kind, the primary indication for this therapy was not signs of increasing toxicity, but symptoms resulting from displacement of the mediastinal structures. This subject has been one of considerable controversy during the past decade. The anatomical findings of Hübsmann (5)

led him to believe that bronchial occlusion played a definite rôle in reducing the size of tuberculous cavities. The clinical observations of Adams and Singer and others were that the tuberculous lesion improved and the symptoms became markedly alleviated with the development of massive atelectasis of the affected pulmonary tissue. Finally one of us (W. E. A.) (7) proved that massive atelectasis brought about by bronchial occlusion from within exerted a favorable influence on experimental pulmonary tuberculosis in dogs.

Excessive exudate prevented closure of bronchi in humans by the nitrate of silver technique. Thus in the following experiments retention of the irritant in the desired location was obtained by injection of the silver nitrate between two ligatures.

Twelve dogs were divided into two groups. In the first group of two dogs the lesions were produced bilaterally. In the second group of ten dogs, a tuberculous lesion was produced in a single lobe. The primary bronchus of the affected lobe was doubly ligated with linen and 0.1 cc. of a 10 or 35 per cent solution of silver nitrate was injected into the bronchus between the two ligatures just before the distal ligature was applied. In the last five dogs the injection of 0.05 cc. of a 10 per cent solution of silver nitrate was made after both ligatures were tied.

Results: One dog died four days after operation due to distemper that existed previous to the ligation. At autopsy the bronchus was occluded. There was reopening in one dog resulting in incomplete obstruction with subsequent production of bronchiectasis. One dog died as the operation was being performed of an overdosage of ether. Two other animals died shortly after operation due to the cauterizing action of the silver nitrate (35 per cent) solution which flowed peripherally into the lung. The procedure was then altered, only a 10 per cent solution being used, only 0.05 cc. being injected and the injection being made after both ligatures had been applied in order to retain the chemical in the desired location. All of the five animals treated in this manner resulted in successful collapse of the pulmonary lobe with no fatalities. The remaining dogs which were kept as long as four and one-half months with complete bronchial occlusion revealed progressive healing of the tuberculous lesions.

The animals were operated from three weeks to two months after the infection and after the lesions had been observed by X-ray examinations.

It was remarkable with what ease the operation could be performed.

FIG. 2A

FIG. 2B

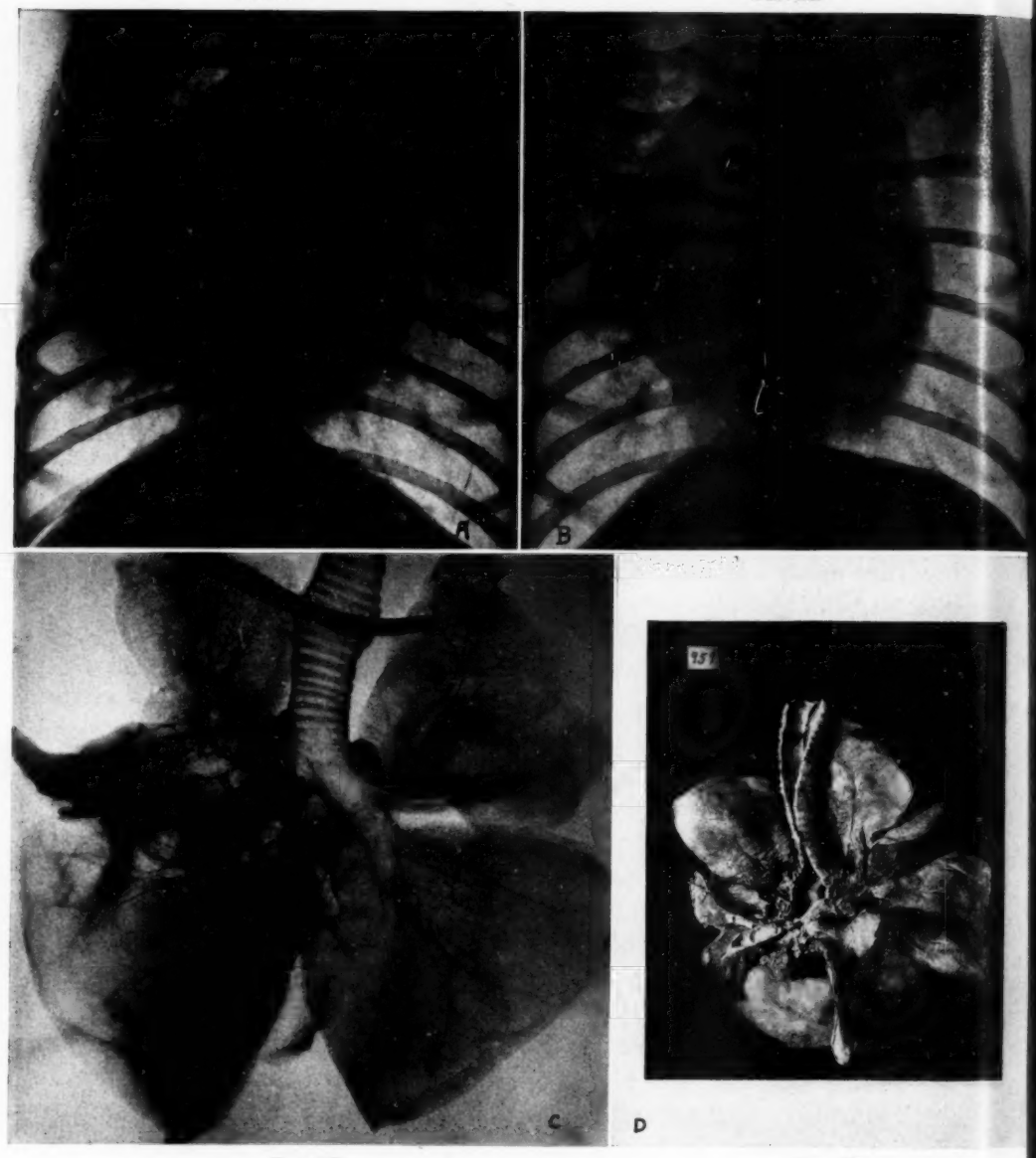


FIG. 2C

FIG. 2D

FIG. 2A. X-ray of chest of dog 959 before bronchial ligation. Observe cavity surrounded by diffuse infiltration in the right middle lobe (lesion one month old).

FIG. 2B. X-ray of chest of the same dog three months after bronchial ligation. Note reduction in size of the affected lobe.

FIG. 2C. X-ray of specimen of dog 959 revealing occlusion of the right middle lobe bronchus and atelectasis of the lobe.

FIG. 2D. Photograph of specimen of the same dog cut open showing the ligature of the right middle lobe bronchus, the distal bronchial dilatation, the atelectasis of the lobe and the healing of the lesion four and one-half months after the operation.

FIG. 3A

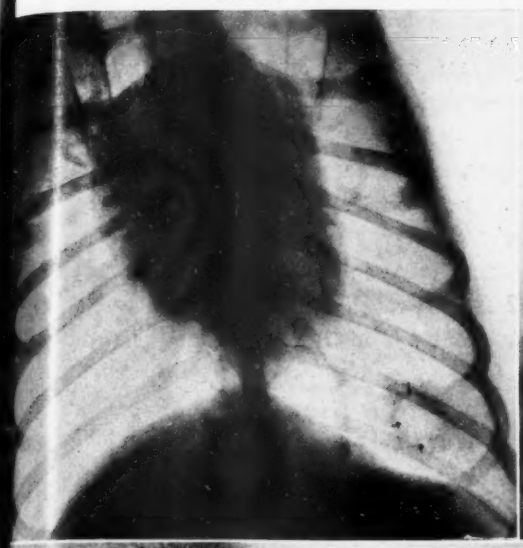
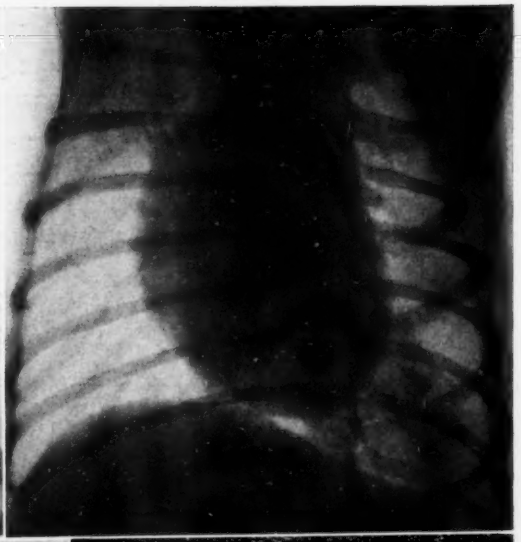


FIG. 3B



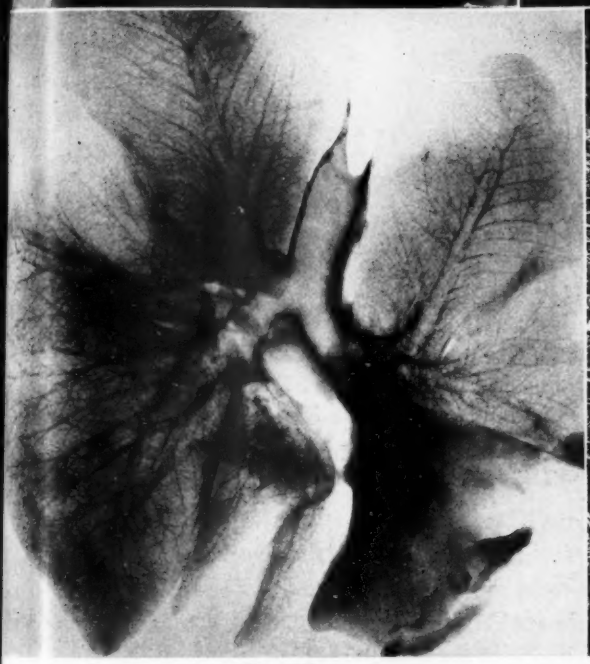


FIG. 3C

FIG. 3D

FIG. 3A. X-ray of chest of dog 687. A circular cavity is seen in the left lower lobe (6 weeks old).

FIG. 3B. X-ray of the same dog six weeks after ligation of the left lower bronchi. Note atelectasis of the left lower lobe.

FIG. 3C. X-ray of lungs of same dog sacrificed 4.5 months following ligation. Note obstruction of bronchus with massive collapse of the left lower lung lobe.

FIG. 3D. Microscopical section of collapsed lobe through area occupied formerly by cavity. Much fibrous tissue surrounding a few microscopical tubercles remains (× 65). A: atelectatic parenchyma; B: fibrous tissue; C: tubercles.

In every case a large lesion was present. In one case (959) diffuse infiltration throughout the lobe surrounded the cavity; adhesions fixed the affected lobe to the chest-wall.

Excepting the ether death, the dogs made an uneventful recovery from the operation. One day after operation they appeared to be in good condition. The postoperative course was closely observed and frequent fluoroscopic and X-ray examinations were made. No pleural effusion was demonstrable (figures 2 A & B and 3 A & B). The cavities rapidly disappeared and the atelectatic lobe became progressively

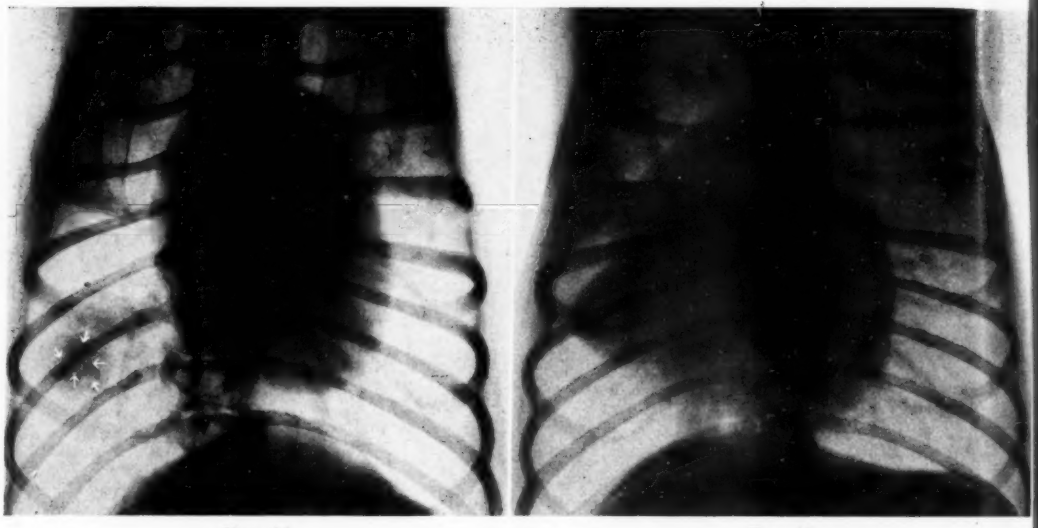


FIG. 4A FIG. 4B

FIG. 4A. X-ray of chest of dog 858 of the unilateral group showing cavity in right middle lobe of 3.5 weeks' duration.

FIG. 4B. X-ray of chest of same dog 2.5 months following collapse of right middle lobe by fascial transplantation.

smaller. The mediastinal structures were deviated somewhat toward the affected side and the diaphragm was elevated. Bronchoscopic examinations were made and bronchial occlusion verified. At autopsy the ligatures were intact and the lobes were atelectatic.

After occlusion the lesion rapidly regressed as demonstrated by X-ray examination and at autopsy three to four months later only a fibrous tissue scar with a few microscopic tubercles existed at the site of the previous cavity (figures 2 C & D and 3 C & D). These results indicate that bronchial ligation and subsequent lung collapse proved efficient in closing the experimentally produced tuberculous lesion.

A postoperative pleural effusion was expected after freeing the adhesions about the diseased lobe but none was observed. A similar observation was made in one case of the fascial transplant groups. In clinical cases, the freeing of pleural adhesions associated with an acute pulmonary infection is apt to produce a marked pleural effusion. By closing the bronchus the danger of bronchial dissemination of the tubercle bacilli into other healthy lobes is obviated. This may result in cases where collapse of lobes harboring bronchogenic cavities is induced where a free bronchial communication exists (880, fascia).

DISCUSSION

The results of collapse therapy in pulmonary tuberculosis are not always those desirable. In 1,128 cases studied by Ulrici (8) there were only 23 per cent of ten-year cures. Consequently the trial of new methods is justifiable.

Theoretically, fascial collapse should aid a pneumothorax very materially in cases of so called "hanging-cavities," where adhesions too large for division with safety prevent complete closure of the cavity. In this way not only would the cavity be completely obliterated but also permanently closed. The closure would be obtained within a very short period of time and would therefore decrease the danger of spread of the disease to another part of the lung and of exposure of others to the infection.

Thoracoplasty and pneumothorax are not infrequently lacking in the treatment of "circular cavities" with a check-valve communication with the bronchial tree. The cavity simply shifts over to the mediastinum when pressure is applied from the side. There is also the danger of mediastinal displacement and compression of the heart and its great vessels. The clinical application of this type of collapse in these cases is worthy of serious consideration.

The fascial transplant maintains complete relaxation of the lobe and produces a centripetal collapse in all directions. The compression is independent of the mediastinal instability; the procedure is not traumatic and does not alter the form of the chest.

Thus, in our experiments, the fascial transplant produces shrinking of the collapsed lobe, prevents progression of the tuberculous infiltration, occludes the cavities and leads to calcification of the lesions. This

method offers a means for collapsing a selected area of lung tissue. Its clinical application may be advisable in selected cases.

By the second method of producing collapse, that is, bronchial ligation, we obtain a passive congestion of the obstructed lung, a proliferation of connective tissue and complete rest of the lung, more complete perhaps than by any other known method. Some clinical cases of pulmonary tuberculosis are not contaminated by secondary infection. In these cases complete occlusion of the bronchus by ligature should prove beneficial to the patient.

Unfortunately one cannot always tell which cases have a mixed infection of the lung. On the other hand the lung can be collapsed to almost the same degree by the fascial transplant method as by bronchial ligation. The efficacy of the treatment of experimentally produced lesions was about the same in both instances. The danger attending the use of the fascial transplant method appears to us to be less than that of the bronchial ligation method. Thus the former is more suitable for clinical applications.

SUMMARY

Two methods of production of collapse of the lung have been applied in the treatment of experimental cavernous pulmonary tuberculosis. One entailed the suturing of a fascial transplant about the diseased lung lobe; the other consisted of doubly ligating the involved lobe bronchus and the injection of a small amount of a solution of silver nitrate between the ligatures.

The treatment of experimentally produced tuberculosis of the lung by these methods was noticeably accompanied by progressive healing of the lesions. After the technique was once developed there was little danger attending the procedures. Their application to clinical cases is discussed.

We wish to thank Dr. Arthur J. Vorwald and Dr. Esmond R. Long for cultures provided for this investigation and Dr. Fred de Peyster and Dr. Omar Fareed for technical assistance.

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DISEASE OF ACCESSORY NASAL SINUSES[1]

Its Incidence in a Tuberculosis Sanatorium

BENJAMIN L. BROCK AND JOSEPH C. BELL[2]

The relationship between nontuberculous pulmonary disease and chronic infection of the upper respiratory tract has been discussed at length in the literature. The frequency with which chronic tracheobronchitis and bronchiectasis occur in the presence of nasal accessory sinus disease and other forms of upper repiratory tract infection has been emphasized. This information should be of interest to the medical profession as a whole but of special interest to those engaged in nose and throat and chest work. Undoubtedly many patients with pulmonary disease of questionable nature are being held in tuberculosis sanatoria over prolonged periods of time before the diagnosis of nontuberculous pulmonary disease is finally made. This is no doubt due to the fact that the usual procedures of diagnosis at our disposal are not adequate in such cases. Experience has taught us that the more facilities which are available for differential diagnosis, the more often will indications for their utilization be found. It follows from this that the correct diagnosis will more frequently be made and adequate treatment instituted without delay. Bronchography and bronchoscopic examination are of inestimable value, and investigation of the nasal accessory sinuses by means of the X-ray has proved very helpful in the differential diagnosis of many of these questionable lung conditions. This does not imply that parenchymatous or even bronchial changes necessarily occur in the presence of nasal accessory sinus disease. The presence of sinus disease or other forms of upper respiratory tract infection, however, is often a helpful guide to the correct diagnosis of the lung condition.

One group of cases admitted to the Sanatorium for differential diagnosis is shown to have a chronic tracheobronchitis caused by a repeated infection from the upper respiratory tract. Other cases admitted with a diagnosis of pulmonary tuberculosis, more particularly those showing upper lobe lesions and a negative sputum, have been proved to have

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[2] Louisville, Kentucky.

bronchiectasis. In such cases a diseased sinus may be the clue to the diagnosis and bronchography or bronchoscopic examination may prove it. Basal lesions in the presence of disease of the nasal accessory sinuses may in many cases point to the latter as the source of infection, and where the diagnosis of uncomplicated bronchiectasis is made the infected sinus should be looked upon as the outstanding cause, although there may be other contributing factors. Kern states that of twenty-one patients with bronchiectasis treated in the University Hospital, Philadelphia, all were proved to have sinus disease on X-ray examination. Clerf reported that 82 per cent of his cases with bilateral bronchiectasis showed sinus disease. McLaurin believes that bilateral bronchiectasis is always associated with disease of the nasal accessory sinuses.

The results of this investigation are based upon the study of 306 adult white patients admitted consecutively to the Waverly Hills Sanatorium during approximately a year's period. In addition to the routine diagnostic procedure, X-ray films of the nasal accessory sinuses were made on these patients at the time of their admission.

Of the 306 patients studied, 253 were found to have uncomplicated pulmonary tuberculosis, so far as the lungs themselves were concerned. Four had pulmonary tuberculosis complicated by bronchiectasis. Sixteen had bronchiectasis alone and 28 were diagnosed as having normal lungs on X-ray examination. Clinically, however, the majority of this latter group were shown to have tracheobronchitis. In addition to the above there were 3 patients with carcinoma of the lung and 2 with pulmonary abscess.

Of the 253 patients found to be tuberculous, 101, or 40 per cent, had disease of the nasal accessory sinuses, slight to extensive in extent. When classified according to sex it was found that 44.1 per cent of the males and 36.2 per cent of the females had sinus involvement. It was also found that the pathological changes in the sinuses were more pronounced in the men, 29.7 per cent of whom had moderate to extensive involvement as compared to 20.7 per cent among the women. Slight mucosal thickening was present in 14.4 per cent of the men and 15.5 per cent of the women.

The group with bronchiectasis alone was of special interest in that there was a very high percentage with sinus disease and practically all of them were men. Of the 16 patients with bronchiectasis 13 were men and 10, or 77 per cent, of them had sinus disease. Of the 3 women with bronchiectasis one had an infected sinus. Of the 4 patients who

had both pulmonary tuberculosis and bronchiectasis, 2 had moderately extensive sinus disease.

The 28 patients in the group classified as having normal lungs on X-ray were also of interest in that the sinus disease in 39.3 per cent of them helped considerably in clearing up the final diagnosis of tracheobronchitis. The question of sex was again a determining factor. Whereas only 4, or 23.5 per cent, of 17 women were shown to have changes in their sinuses, 7, or 63.7 per cent, of 11 men were so diagnosed. Again it was found that, whereas extensive sinus disease was the rule in the bronchiectasis group, no cases with very extensive sinus involvement were found in the group with tracheobronchitis. Since these patients are considered to be potential cases of bronchiectasis, it is extremely important from their

TABLE 1

Incidence and degree of sinus involvement in 253 adult white patients with pulmonary tuberculosis classified according to sex

		NEGATIVE	POSITIVE	SLIGHT	MODERATE	EXTENSIVE	MODERATE AND EXTENSIVE COMBINED
Women	135	86	49	21	17	11	28
	53.3%	63.8%	36.2%	15.5%	12.6%	8.1%	20.7%
Men	118	66	52	17	20	15	35
	46.7%	55.9%	44.1%	14.4%	17.0%	12.7%	29.7%
Total	253	152	101	38	37	26	63
	100.0%	60.0%	40.0%	15.1%	14.6%	10.3%	24.9%

standpoint that early diagnosis and treatment of the sinus disease be accomplished in order to prevent progressive changes in the bronchi.

The three patients with carcinoma of the lung were men. The sinuses were normal in two of them and moderately extensive disease was present in the other. Of the two patients with lung abscesses, one was a man and the other a woman. The sinuses were normal in both of them.

The region in and around Louisville, Kentucky, from which our patients are drawn, is situated in the Ohio River Valley where the altitude is about four hundred feet above sea level and where the atmosphere is very humid. Although 40 per cent of our tuberculous patients have been shown to have sinus disease we felt that this would prove to be a higher incidence than that to be found among the general population. The small group of 28 individuals discussed in this paper as having

normal lungs on X-ray could not rightfully be used as a control since most of the patients in the group were admitted to the Sanatorium because of symptoms referable to their lungs. Of these patients 39.3 per cent had sinus disease and we assume that the sinus disease was responsible for the chest symptoms in most of them. Other types of infections of the upper respiratory tract accounted for most of the others. In order to determine whether or not pulmonary tuberculosis renders an individual more susceptible to sinus infection, a study of the sinuses in a group of 50 nontuberculous employees in the Sanatorium was made. Twenty-five of these were men and 25 were women. These individuals were not questioned regarding possible sinus infection previous to the X-ray examination since it was thought that such a selection would be more

TABLE 2

Incidence and degree of sinus involvement in 50 adult white patients (controls with no evidence of pulmonary tuberculosis) classified according to sex

		NEGATIVE	POSITIVE	SLIGHT	MODERATE	EXTENSIVE	MODERATE AND EXTENSIVE COMBINED
Women	25	19	6	0	3	3	6
	50.0%	76.0%	24.0%	0.0%	12.0%	12.0%	24.0%
Men	25	17	8	1	4	3	7
	50.0%	68.0%	32.0%	4.0%	16.0%	12.0%	28.0%
Total	50	36	14	1	7	6	13
	100.0%	72.0%	28.0%	2.0%	14.0%	12.0%	26.0%

representative of the general population. Of the 50 employees 14, or 28 per cent, were found to have sinus involvement. Eight, or 32 per cent, of the men and 6, or 24 per cent, of the women were so affected. Since 44.1 per cent of the men and 36.2 per cent of the women in the tuberculous group had sinus disease it would appear that pulmonary tuberculosis in some way renders an individual more susceptible to sinus infection. This is probably due to the low state of resistance reached by tuberculous patients during the several weeks or months prior to hospitalization. On the other hand it has been suggested that chronic sinusitis may result directly from repeated spraying of the nasal chambers by coughed-up infected material in various lung diseases, including pulmonary tuberculosis.

Of the 253 patients, 29.7 per cent of the men and 20.7 per cent of the

women were found to have moderate to extensive sinus involvement. Of the 50 nontuberculous controls, 28 per cent of the men and 24 per cent of the women were similarly affected. Although it has been shown that pulmonary tuberculosis definitely affects the total incidence of sinus disease, we conclude from the above figures that this disease does not cause an increase in the incidence of advanced sinus disease. The

TABLE 3

Incidence and degree of sinus involvement in 102 adult white patients with moderately advanced pulmonary tuberculosis classified according to sex

		NEGATIVE	POSITIVE	SLIGHT	MODERATE	EXTENSIVE	MODERATE AND EXTENSIVE COMBINED
Women	59	36	23	13	6	4	10
	57.8%	61.0%	39.0%	22.0%	10.2%	6.8%	17.0%
Men	43	21	22	9	7	6	13
	42.2%	48.8%	51.2%	21.0%	16.2%	14.0%	30.2%
Total	102	57	45	22	13	10	23
	100.0%	56.0%	44.0%	21.5%	12.7%	9.8%	22.5%

TABLE 4

Incidence and degree of sinus involvement in 136 adult white patients with far advanced pulmonary tuberculosis classified according to sex

		NEGATIVE	POSITIVE	SLIGHT	MODERATE	EXTENSIVE	MODERATE AND EXTENSIVE COMBINED
Women	63	41	22	6	10	6	16
	46.3%	65.0%	35.0%	9.6%	15.8%	9.6%	25.4%
Men	73	43	30	8	14	8	22
	53.7%	59.0%	41.0%	10.9%	19.2%	10.9%	30.1%
Total	136	84	52	14	24	14	38
	100.0%	61.8%	38.2%	10.3%	17.6%	10.3%	27.9%

increase in the total incidence of sinus disease in the tuberculosis group is made up entirely of those patients with slight mucosal thickening.

The tuberculous patients in this study, however, were further classified into minimal, moderately advanced and far advanced groups to determine if possible whether the extent of pulmonary tuberculosis affects the incidence of sinus infection and also whether it affects the degree of pathological change in the sinuses. Of the 253 tuberculous patients,

15 were in the minimal stage and 33.4 per cent of them had pathological changes in their sinuses. Twelve of the 15 patients in this group were women, 4 , or 33.4 per cent, of whom had sinus disease. Only 3 were men and one of them had a positive sinus. Relatively very few men are admitted to this institution in the minimal stage of tuberculosis, due perhaps to the fact that they are the bread earners and therefore delay their entrance until they are in the advanced stage. Since sinus disease has been shown to be predominantly among men it is felt that the percentage of sinus disease in this group would have been higher had there been a greater number of men comprising it.

In the moderately advanced group of 102 patients, 39 per cent of the women and 51.2 per cent of the men had definite pathological changes in their sinuses, whereas in the far advanced group of 136 patients 35 per cent of the women and 41 per cent of the men had sinus disease. Certainly, if extent of pulmonary tuberculosis influences the incidence of sinus infection, the figures in these two groups should have been reversed.

On the other hand we have considered only those patients with pulmonary tuberculosis showing more than slight mucosal thickening, or in other words those showing moderate to extensive pathology in the sinuses, in order to determine what affect extent of pulmonary disease has upon extent of sinus involvement. In the groups of minimal, moderately advanced and far advanced pulmonary tuberculosis, moderate to extensive sinus disease was found in 33.4 per cent, 30.2 per cent and 30.1 per cent of the men, and in 16.8 per cent, 17.0 per cent and 25.4 per cent of the women, respectively. Although it is suggestive in the far advanced group of women, it would appear that degree of sinus infection is not influenced definitely by degree or extent of pulmonary tuberculosis. On the other hand it appears that the higher incidence of sinus disease and the higher incidence of advanced changes in the sinuses among men as compared to women is probably due to the unsheltered life of the former. Greater exposure to unfavorable weather conditions and various irritants in industry are no doubt conducive to repeated infection in the upper respiratory tract.

COMMENTS CONCERNING THE X-RAY EXAMINATION OF SINUSES

We recognize that our examinations in the above cases cannot be taken as an accurate determination of the incidence of sinus disease. This is due, in part, to the fact that the diagnosis in each case was based on the findings from a single set of stereoscopic films made in the Waters'

position. This of course does not constitute a complete X-ray examination of the nasal accessory sinuses. However, cost had to be considered and experience has shown that this routine will suffice to make the diagnosis of sinus infection in at least 90 per cent of the cases in which X-ray changes can be demonstrated by the complete examination. The anterior sinuses are well shown in this position but the posterior ones may not be. It is rare, however, to find the posterior sinuses infected when the anterior ones are normal. This does occur in rare instances and accounts in part for the error in our determination of the true incidence of infection.

Some may question whether the diagnosis of sinus disease from an X-ray examination is at all accurate, but experience has shown when the findings are properly interpreted by a competent radiologist that they parallel closely the clinical ones.

The above statement has been discussed with two of the local leading specialists in diseases of the nasal accessory sinuses. They concurred in the opinion above expressed and further stated independently that were routine X-ray and clinical examinations done on a group of patients the diagnosis would agree in at least 90 per cent of the cases.

We have interpreted mucosal thickening as evidence of sinus disease. No attempt has been made to say whether this thickening is the result of past infection which is inactive or whether it is due to active disease. Sinuses with mucosal thickening undergo recurrent periods of active infection interspersed with periods of apparent quiescence, and for this reason it would seem they should be considered a potential source of infection. The part that allergy may play in mucosal changes cannot be determined from the X-ray films. Whether the allergic change is primary and the infectious change secondary or *vice versa* is an open question, but it would seem that they often go hand in hand.

CONCLUSIONS

From this study it is concluded that the investigation of the nasal accessory sinuses by means of the X-ray serves as a helpful guide in the differential diagnosis of cases with questionable lesions in the lungs or with definite lesions of doubtful origin. When sinus disease is found to be present in such cases conservative or radical treatment of the sinus condition may not only prevent the development of bronchiectasis in individuals with tracheobronchitis but may well help to prevent further extension in patients already having bronchiectasis.

The incidence of nasal accessory sinus disease is not only much higher among men than among women but the disease has been found to be more extensive among men.

Tracheobronchitis and bronchiectasis have also been found to be much more common among men than among women. Tracheobronchitis is accompanied in a large percentage of cases by sinus disease, but when bronchiectasis exists sinus disease is the rule.

Disease of the nasal accessory sinuses occurs in a large percentage of the patients admitted routinely to the Sanatorium. The incidence of sinus disease in a group of nontuberculous and otherwise apparently healthy employees in the Sanatorium was considerably lower than that found in the tuberculous group. We conclude, therefore, that pulmonary tuberculosis renders an individual more susceptible to sinus infection. From the study, however, it can be further stated that the *amount* of pulmonary tuberculosis *per se* has little or no influence upon the *incidence* or upon the *amount* of sinus disease in any given group.

We wish to express our appreciation of Dr. Lawrason Brown's helpful criticism of this paper.

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BRONCHIAL OCCLUSION DUE TO TUBERCULOUS LYMPHADENITIS[1]

LEO V. SCHNEIDER

In infancy, bronchial stenosis and bronchial obliteration caused by extrinsic pressure of large tuberculous lymph nodes adjacent to bronchi are comparatively uncommon. The clinical picture may resemble and suggest the presence of a foreign body in the bronchus. Wheezing respiration, dyspnoea, cough, and other physical signs are responsible also for the diagnosis of bronchial asthma, often probably made erroneously on the basis of these clinical signs. There is, therefore, a strong possibility that some of the asthmatic conditions are actually cases of bronchial stenosis. Diagnostic bronchoscopy and roentgen ray studies of the chest are of great importance in order to arrive at a correct diagnosis.

Case Report

A poorly nourished colored baby, age 9 months, was admitted to Glenn Dale Sanatorium July 21, 1937, with a diagnosis of "tuberculosis and bronchial asthma." The essential features of the clinical history obtained at that time were that on June 1, 1937, the child was taken ill with a cold, had a fever and difficult breathing. The mother took the child to a clinic where he was examined several times during a period of three weeks, and, finally, hospitalization was advised because the child did not show much improvement. He was taken to a general hospital, kept there under observation and treatment for one month, and then referred to Glenn Dale Sanatorium with the above mentioned diagnosis.

Family history suggested exposure to active pulmonary tuberculosis since the child was born, living in the same house with his aunt who died of this disease April 24, 1937. The father was examined at the chest clinic, but no diagnosis of tuberculosis was made; the mother has not been examined, but the tuberculin test was positive, and she was requested to come to the clinic for X-ray and physical examination.

On admission the child looked ill and had difficulty in breathing, his respiration being definitely labored and accompanied by loud wheezing and a crowing type of inspiration.

[1] From the Glenn Dale Sanatorium for the District of Columbia, Glenn Dale, Maryland.

On examination the following physical findings were noted: limitation of motion on the right side of the chest, dull percussion note and bronchial breathing over the right upper lobe posteriorly and in the axilla, and increased vocal resonance; on the left side breath-sounds were increased throughout; wheezes scattered throughout the chest and a loud inspiratory stridor with some retraction of chest. Laboratory findings were of little importance. A "gag" specimen was negative for tubercle bacilli. Haemoglobin was 85 per cent with 5,100,000 red cells. There was polymorphonuclear leucocytosis. Wassermann and Kahn reactions were negative. Sedimentation rate was 6.8 mm. in sixty minutes. Tuberculin was three plus. A roentgenogram of the chest taken on admission showed an opaque area of the upper half of the right side. There was also seen a large circular area of opacity in the lower right with mottled infiltration about these areas. Roentgen ray study of the chest revealed changes not unlike those seen in atelectasis, which, together with wheezing respiration and other physical findings described, strongly suggested the diagnosis of bronchial obstruction. Laryngoscopy revealed nothing abnormal in the epiglottis, cords or arytenoids. Diagnostic bronchoscopy was done July 30, 1937, ten days after admission. The shape and topography of the right bronchus were somewhat distorted, the wall of the bronchus was rigid and somewhat thick, and the lumen was completely obliterated. The bronchus at the bifurcation was congested, and, although the character of the pathological lesion could not be determined bronchoscopically, it manifestly was not bronchial asthma. It was difficult to decide between intrinsic stenosis caused by tumor, inflamed masses or scars, and extrinsic stenosis due to pressure from tuberculous lymphadenitis. A large amount of tenaceous mucus was aspirated, examined, and found negative for tubercle bacilli on direct smears and on cultures. Following bronchoscopy, the child was extremely dyspnoeic due to the transient laryngeal oedema caused by instrumentation, and the degree of obstruction was such as to prevent any adequate relief from the inhalation of oxygen. However, several days later the child seemed to rally, he took nourishment better, his breathing was easier, and the laryngeal oedema gradually subsided.

Due to obstruction of the right bronchus and weakened respiratory movements, there was a periodic accumulation of mucus, which was aspirated on numerous occasions. The child lost some weight but was fairly comfortable until October 8, 1937, when he suddenly developed symptoms of acute bronchopneumonia. He was dyspnoeic, and inspiration was attended by peculiar noisy whistling sounds; he was cyanotic and had a dry, barking and somewhat paroxysmal cough. Physical signs at this time were dulness, diminished vocal fremitus due to filling up of the lung with secretion, scattered râles over consolidated areas situated chiefly on the right side and to a lesser extent on

FIG. 1

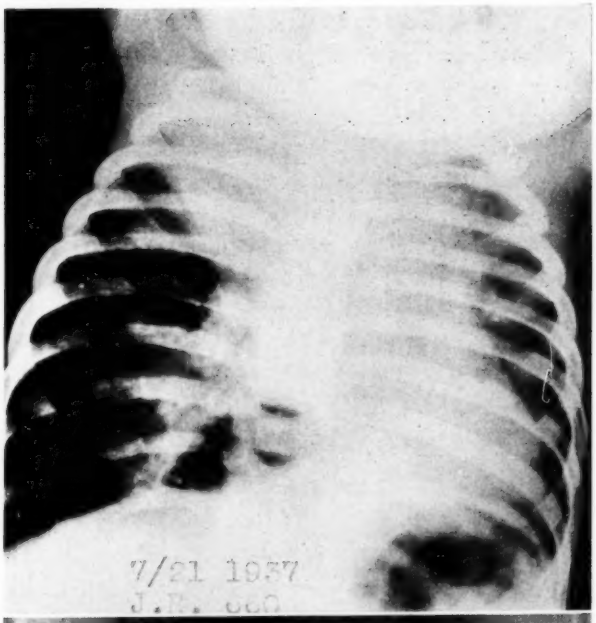

FIG. 2

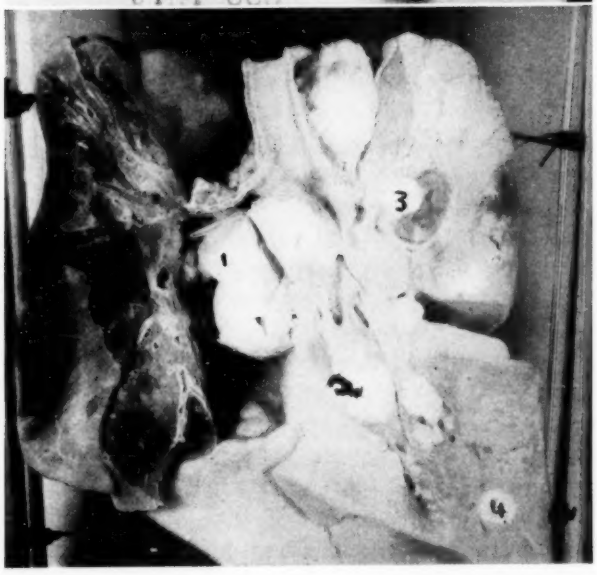

FIG. 1. J. R. 660 July 21, 1937. X-ray of chest on admission

FIG. 2. J. R. 660 October 27, 1937. Lungs removed at autopsy. (1) Caseation of tracheobronchial lymph node, resulting in complete block of bronchus. (2) Caseation of bronchopulmonary lymph node. (3) Caseous material removed. (4) Consolidation in lower lobe.

the left. He was in a stuporous, toxaemic state with a pulse of 150 to 164 and respiration 50 to 70. He died October 27, 1937.

Postmortem examination: The following findings were noted at autopsy: There is marked emaciation and no peripheral oedema. The fontanelles are partially closed. The pupils are dilated and equal. The posterior cervical lymph nodes are enlarged; they are discreet and freely movable.

The chest shows prominent ribs due to the marked emaciation. The thoracic viscera are in normal relationship with one another. The thymus gland is average in size and shape. The heart is average in size and shape and presents no abnormalities. The outstanding feature in the thoracic cavity is a large, conglomerate mass of tracheobronchial lymph nodes which projects particularly to the right of the midline. This mass is approximately 11 x 7 cm. and the cut surface shows diffuse caseation. The mass encroaches on the main right bronchus producing a complete occlusion in practically its entire course. This has produced a complete atelectasis of the entire upper right lobe. The latter appears as a firm, nonelastic, airless mass presenting on the cut surface a steel-blue appearance. There are some pleuropericardial adhesions. The middle and lower lobes of the right side show a diffuse recent bronchopneumonia and a recent fibrinous pleural exudate. The left lung shows emphysema involving both lobes which is evidently compensatory in type. The cut surface is pinkish-gray and there is no evidence of inflammatory disease. The pleura of the left side is smooth and glistening throughout.

Pathologic diagnosis: (*1*) Tuberculosis of the tracheobronchial lymph nodes, producing pressure obliteration of the right main bronchus with atelectasis of the right upper lobe. (*2*) Recent acute bronchopneumonia, middle and lower right lobes. (*3*) Compensatory emphysema, left upper and lower lobes.

CONCLUSIONS

A case of bronchial obliteration caused by pressure of large tuberculous lymph nodes is presented. The significance and importance of differential diagnosis between asthma, foreign body, and bronchial stenosis are pointed out. In all probability, the manifestation began in an acute manner; the child suffered from extensive tuberculous lymphadenitis, and as he gradually developed asthma-like symptoms, a diagnosis of asthmatic hypersensitiveness was suggested. This erroneous conclusion may easily take place if we will consider that in childhood asthma is a rather frequent manifestation, particularly the asthmatic bronchitis type. The latter form is still more frequent in infancy. When a bronchus is entirely obstructed by scar tissue, a persistent lobar atelectasis may result. This is sufficient to cause expiratory dyspnoea and other

mechanical changes resulting in decompensation of the respiratory and circulatory systems. Diagnostic bronchoscopy is of great help, though it may be difficult to decide between intrinsic stenosis produced by foreign bodies or tumors and extrinsic stenosis from pressure of extensive hilar lymph nodes.

I wish to express my appreciation to Dr. D. L. Finucane, Superintendent of Children's Sanatorium, Glenn Dale, Maryland, for his interest and coöperation and to Dr. David Davis for the bronchoscopic data.

ANAEMIA AS A PREDISPOSING FACTOR IN TUBERCULOSIS

CECILIA SHISKIN[1] AND S. ROODHOUSE GLOYNE[2]

As long ago as the seventeenth century Richard Morton expressed the view that anaemia often passed into consumption by imperceptible degrees. There appears to be no direct experimental evidence, however, as to whether anaemia really acts as a favorable soil for the development of tuberculosis. The experiments recorded here were undertaken to investigate the question.

TECHNIQUE OF EXPERIMENTS

Various methods have been employed for the production of anaemia in healthy rabbits, such as the administration of phenylhydrazine hydrochloride (Price-Jones, 1911), colloidal lead and phenylhydrazine (Whitby and Britton, 1933) and venesection (Price-Jones, 1911).

The method used in these experiments was that of venesection (auricular vein). This method of inducing anaemia by haemorrhage was used by Whipple and his coworkers in dogs in their experiments for the determination of the action of iron salts and liver extracts on blood regeneration.

Rabbits were chosen for the present work, because of their suitability for subsequent experiments with the tubercle bacillus. Healthy adult rabbits from 2 to 3 kilograms in weight were used and amounts of blood from 50 to 111 cc. were withdrawn at one sitting without causing any upset other than temporary shock.

OBSERVATIONS ON POSTHAEMORRHAGIC ANAEMIA IN RABBITS

The following observations were made on the animals before and after bleeding and prior to infecting them with tubercle bacilli.

pH values: In a previous communication (Shiskin, 1936) investigations on the pH values of the blood of healthy rabbits were recorded. In these animals the pH was found to vary from 7.21 to 7.50 with an

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average of 7.34. In the present investigation, in 109 estimations on 36 healthy rabbits the pH varied from 7.18 to 7.41 with an average of 7.31. This is a wider range of variation than was found by one of us (C. S., 1937) in healthy human beings, using the same technique. In rabbits, excitement generally leads to a lower pH; the more placid the animal the more constant its pH. The effect of posthaemorrhagic anaemia on the pH values of venous blood in healthy rabbits, where a single bleeding had been performed, and where there had been repeated bleedings, was investigated in 20 animals.

Haemoglobin percentage and pigment volume: In our experiments the haemoglobin percentage was estimated by Haldane's haemoglobinometer, while the method used for the determination of blood and plasma volume was that of Keith, Rowntree and Geraghty (1915). The pigment volume was obtained by multiplying the percentage of haemoglobin (expressed as a fraction of 100) by the total blood volume. It was not possible to make blood volume estimations in all cases.

Results and Discussion

The effect of bleeding on the pH value of rabbit's plasma: Reference to table 1 shows that in 75 per cent of the cases where records of the pH were obtained both before and after bleeding there was a marked fall in pH immediately after bleeding, irrespective of the amount of blood withdrawn. This fall in pH appeared to be related to the state of the veins at the conclusion of the experiment. Usually at the end of the bleeding the rabbit's ears are cold and the veins are collapsed. In the few instances where the ears remained warm and the veins prominent no change in pH was noted after the bleeding. Furthermore, where the bled ear was cold and its veins were collapsed but the other ear remained warm, a specimen obtained from the warm ear showed no change in pH.

Only 20 records immediately after bleeding were obtained because the collapse of the veins at the end of the experiment made it very difficult to secure a specimen. The change in pH immediately after the bleeding varied from .06 to .30 in 15 out of the 20 specimens examined. In two samples the change was .02 which is within the limits of experimental error. The ears in these instances were warm and the veins remained prominent. In two other cases there was no change in pH after the bleeding, and yet in one of them as much as 111 cc. of blood were withdrawn—equivalent to 45.1 per cent of its total circulating blood volume. But again at the end of the bleeding these rabbits'

ears remained warm and the veins prominent. In a fifth animal the pH remained unaltered but the specimen after bleeding was obtained from the uninjured ear which was warm and had prominent veins.

A reduction in blood pH immediately after severe haemorrhage was also observed by Tatum (1920), Bennett (1926) and Riegel (1927).

TABLE 1

Changes in pH following bleeding

RABBIT	BEFORE BLEEDING	AMOUNT OF BLOOD WITHDRAWN			IMMEDIATELY AFTER BLEEDING	
	pH	Total	Per kilogram of body weight	Percentage of circulating volume	pH	Alteration in pH value
		cc.	*cc.*			
S 23	7.41	48	15.2	—	7.32	−.09
S 29	*7.27*	45	14.2	—	7.21	−.06
	7.27	*75*	23.7		*7.13*	−.14
S 38	7.27	80	25.8	46.5	7.08	−.19
S 39	7.27	111	34.2	45.1	7.27	.00*
S 40	7.31	80	25	34.3	7.25	−.06
S 44	7.37	42	21		7.25	−.12
S 45	7.30	42	19.6		7.21	−.09
S 31	7.15 Exc	58	18.8	41	7.05	−.10
S 20	7.35	84	26.3		7.18	−.17
S 8	7.28	36	16.7		7.18	−.10
	7.27	28.5	10		7.21	−.06
S 11	7.36	51	18.1		7.28	−.08
After inoculation	7.37	21	7.4		7.27	−.10
	7.33	22	7.5		7.26	−.07
	7.30	45	15		7.28	−.02*
	7.36	48	14.1		7.34	−.02
S 15	7.35	60	17.4		7.05	−.30
	7.32	51	14.8		7.32	.00
	7.32	63	18.3		7.32	.00†
S 17	7.35	91	31.9		7.21	−.14

* Veins not collapsed.

† Blood taken from the other ear.

Readings of .02 are regarded as within limits of experimental error.

The latter ascribes the acidosis to excessive lactic acid production, due presumably to inadequate oxygenation in the tissues. We would ascribe the fall in pH to shock as in its absence no fall in pH was observed, no matter how severe the haemorrhage induced. Chemical changes other than fall in pH accompanying shock have not been investigated.

On the day following the bleeding, when the rabbit was, as a rule,

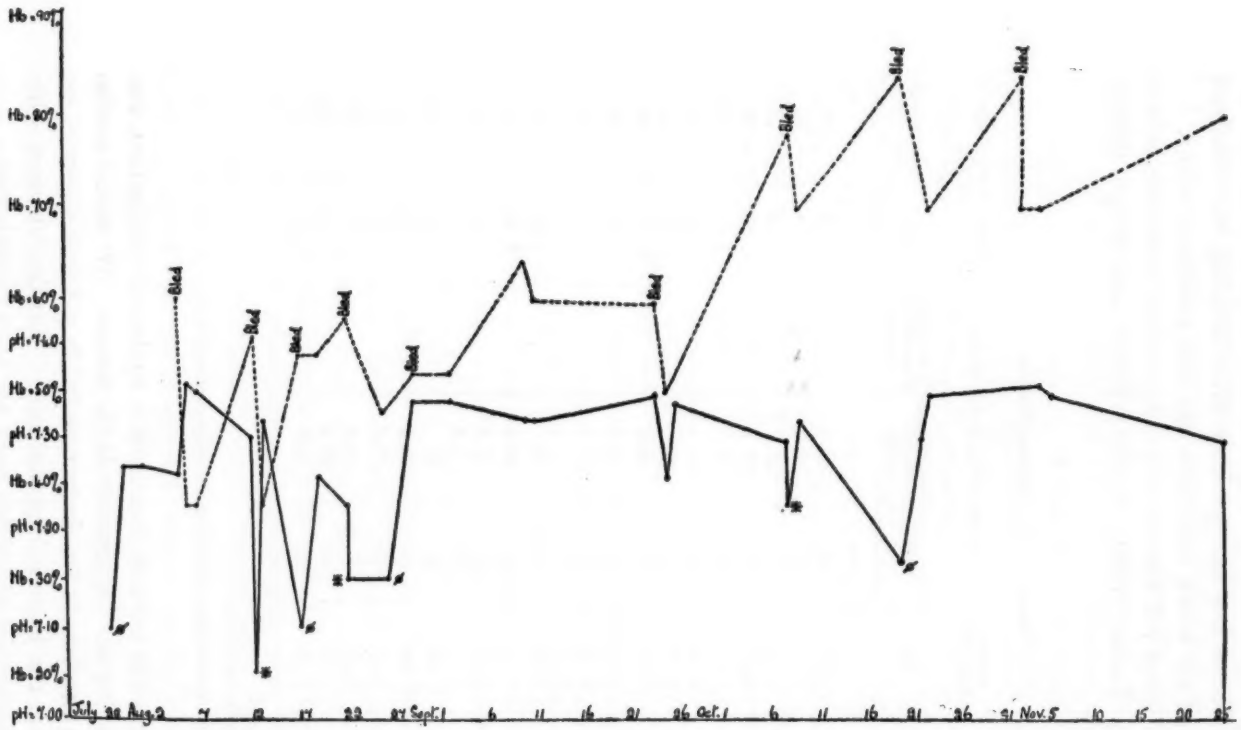

CHART 1. Animal bled nine times (11–48 cc.) in 112 days (intervals between bleedings 5–16 days); total blood withdrawn 276 cc. Weight at commencement 2.216 kilograms, at end 3.401 kilograms (increase 54 per cent). pH before bleeding commenced 7.26, at end of experiment 7.30 (no appreciable change). Hb percentage before bleeding commenced 60, at end of experiment 80 (increase 33.3 per cent).

——— = pH value.

---------- = Hb percentage.

Ø = animal excited.

* = record made immediately after bleeding.

remarkably quiet, a return to a higher pH was noted. Bennett (1926) has also reported a higher pH on the day following a severe haemorrhage. On subsequent examinations the pH varied as with unbled healthy rabbits.

It may be deduced, therefore, that the pH value bears no relationship to the amount of blood withdrawn or to the haemoglobin content of the blood. This is illustrated in a sample curve in chart 1. The finding is in accordance with that of Emerson and Helmer (1935) in patients with pernicious anaemia. These workers state that "the condition of the acid-base equilibrium in pernicious anaemia is independent of the clinical status and is essentially normal." Peters and Van Slyke (1932) also find from the work of Evans (1921) and from other available data on anaemia that the condition of itself has no influence on the acid-base balance of the blood.

That the withdrawal of as much as 45 per cent of the total circulating blood volume should have no effect on the pH is especially noteworthy when we consider that, next to bicarbonate, haemoglobin is the most important buffer agent of the blood. It would appear, therefore, that in the healthy rabbit the mechanism for maintaining the acid-base balance in the blood is capable of dealing with sudden emergencies.

Blood pigment regeneration after bleeding: In one rabbit, three weeks after withdrawing nearly half (45.1 per cent) of the total circulating blood volume at one sitting, regeneration of the blood pigment volume was complete. In another (handicapped, as we subsequently found, by parasitic disease) in which 46.1 per cent of the total circulating blood volume was removed at one sitting, the blood pigment volume was restored to 75.4 per cent of its initial value in 27 days. This is in accordance with the findings of Whipple and his coworkers (1920) who, as already stated, found that in dogs blood regeneration to normal is effected in from 4 to 7 weeks after bleeding one-fourth of the circulating blood volume on two successive days.

POSTHAEMORRHAGIC ANAEMIA AND TUBERCULOSIS

A number of experiments were made on rabbits by bleeding and then inoculating them with virulent tubercle bacilli (bovine or human); 36 rabbits were used, 18 of which were both bled and inoculated, and 17 were inoculated but not bled and one bled but not inoculated, which served as controls. Space does not permit of a full record of all the investigations carried out, which are summarized below.

Infection with human strain of tubercle bacilli: A fully virulent human strain "B" was injected subcutaneously in doses of 400 million organisms, the animals having first been bled. Three rabbits were inoculated, each with a corresponding control animal which was also inoculated but not bled. The weights of the animals ranged from 1.48 to 2.82 kilograms. The blood was withdrawn at intervals as follows:

No. 8772: 14 bleedings of 34–54 cc. in 6 months
No. 8767: 10 " " 17–55 cc. " " "
No. S11: 8 " " 22–53 cc. " 2½ "

The lowest haemoglobin percentage recorded after bleeding was 38.

At the end of each experiment, the rabbit which had been bled showed rather less advanced lesions than did the controls. The experiment was then repeated by withdrawing 92 cc. of blood from a rabbit (S42) of 3.20 kilograms weight, at one sitting, and immediately afterward inoculating the animal with 20,000 million bacilli intravenously while the lung was still partially depleted of blood. A control animal was also injected with the same dose of organisms but not bled. Both animals were killed four hours later. The lungs of the bled animal were much paler than those of the control, but no difference in tissue reaction was noted apart from a collapse of the capillaries in the lung of the bled animal consequent on the rapid reduction of blood volume.

The anaemia induced by bleeding, therefore, failed to break down the rabbit's well known resistance to the human strain of tubercle bacillus injected subcutaneously, while a rapid depletion of blood in the lung failed to produce any noticeable difference in tissue reaction to a very large dose of tubercle bacilli injected intravenously.

Infection with bovine strain of tubercle bacilli: A fully virulent bovine strain was employed. The number of bacilli injected was varied, from 400,000 organisms to 3,000 million, some of the inoculations being made subcutaneously and others by the intravenous route. Thirteen rabbits were used with an equivalent number of controls. The weights of the animals ranged from 2.21 to 3.45 kilograms. The blood was withdrawn at different intervals as follows: (*1*) several bleedings in one week; (*2*) numerous bleedings spread over a period of several weeks. The maximum withdrawal of blood was three in one week in amounts ranging from 26 to 63 cc.; the largest amount withdrawn at one sitting was 92 cc. and the smallest 20 cc. These amounts were controlled in some of the experiments by estimations of blood volume before and after bleeding. The

lowest percentage of haemoglobin recorded was 35. In some instances the withdrawal of blood was carried out first and the bacilli injected afterward, while in others the injection was made during the course of the experiments. The animals were killed at intervals from four hours to eight weeks after inoculation.

The results were for the most part equivocal. In one instance in which a rabbit of 2.85 kilograms weight was inoculated intravenously with 400 million bacilli immediately after the withdrawal of 82 cc. of blood and then killed four hours later, the lung juice showed a greater leucocytic response than did that of the control animal. Of the animals which were allowed to survive for longer periods, the majority of those bled showed somewhat more advanced disease than did the controls, but the differences could not be regarded as significant. We may, therefore, conclude that the degree of anaemia we were able to induce by bleeding healthy rabbits did not produce a significantly increased predisposition to experimental tuberculosis.

Results and Discussion

pH values in tuberculosis: The average pH obtained in 220 estimations on 26 rabbits infected with tuberculosis was 7.315 with variations from 7.10 to 7.43. This differs but little from the figures obtained in 109 estimations on 36 normal rabbits in which the average pH was 7.31 with variations from 7.18 to 7.41. These figures are comparable with those previously recorded by one of us (C. S., 1936). On comparing the pH before and after infection in individual rabbits we find no change in pH after infection in 2 (1 bled and 1 unbled), increase in pH in 10 (4 bled and 6 unbled) and decrease in 10 (8 bled and 2 unbled).

In the remaining 4 rabbits no estimations were made on the pH of the blood before infection. Their average pH values after infection were 7.27, 7.31, 7.33 and 7.29, which values are within normal limits.

There appeared to be no evidence from our experiments, therefore, that infection with bovine tubercle bacilli had any effect on the pH of rabbits' blood.

Des Ligneris (1932) noted an increased alkalinity in the blood of fowls infected with avian tuberculosis and Sasano (1935) found that, in man, strict bed cases of tuberculosis had a slightly higher pH than normal controls. Wiese (1936) found no extreme variations from that of normal in human subjects. Investigations on human subjects by one of us (C. S., 1937) also failed to yield evidence that the pH of the

blood of tuberculous patients differed materially from that of normal controls or from that of patients suffering from other diseases. It is possible, therefore, that the relatively high pH noted by Sasano and Des Ligneris can be attributed to the restricted activity of the patients and of the fowls. Thus we always found a relatively higher pH on the day following bleeding in rabbits when the animals were exceptionally quiet. Yet this relatively high pH was not a permanent alteration as subsequent estimations showed.

Effect of alteration of pH value on tuberculous infection: Investigators differ as to the optimum pH value for the growth of the tubercle bacillus *in vitro*.

Ishimori (1924) finds the human type of the tubercle bacillus *in vitro* prefers a medium with a more alkaline reaction than the bovine bacillus. He gives the optimum pH for growth of the human type as from 7.4 to 8.0 and for the bovine variety as from 5.8 to 6.9. Other workers, on the other hand, have not noted this marked difference between the two types of bacilli as regards optimum pH for growth. Dernby and Näslund (1922) give the optimum pH for both types as from 6.0 to 6.5, while Borrel and his coworkers (1922) record the optimum pH for the human variety as 6.9 and for the bovine 7.0. They also state that there is a narrower pH range for growth with the human than with the bovine type. Griffith (1930), on the other hand, states that the optimum pH for growth of the tubercle bacillus *in vitro* is from 7 to 7.6 and does not mention any difference in this connection between the two types of bacilli. Wells and Long (1932), in summarizing the work of a number of observers, note that in laboratory growth the tubercle bacillus has a much wider growth range than in the animal cell, extending approximately from a pH of 5.5 to 8.2.

We, therefore, tried to investigate this point *in vivo* by inoculating one rabbit intravenously with 4,000,000 bacilli (bovine) immediately after inducing a haemorrhage when its blood pH was relatively low, namely, 7.25, as compared with its normal pH of 7.37, and by inoculating a second rabbit with the same dose and by the same route on the day after inducing the same degree of haemorrhage when the blood pH was relatively high, namely, 7.35. The latter animal died 98 days after inoculation and at autopsy was found to have wide-spread tuberculous lesions involving both kidneys, the spleen, liver, lungs and pleurae. The former had to be killed 83 days after inoculation because it developed

paralysis of its hind legs. At autopsy there were wide-spread tuberculous lesions involving the lumbar lymph nodes, left kidney, spleen, liver and lungs. One cannot do otherwise than conclude that the tubercle bacillus succeeded in thriving equally well in the two rabbits in spite of the initial difference in their blood pH. After inoculation, the blood pH of the two rabbits became and remained almost identical. Had it been possible to maintain the initial difference in the blood pH of the two rabbits subsequent to inoculation it is conceivable that the result might have been otherwise.

The effect of tuberculosis on the anaemia: Our experiments showed that in the case of the simple anaemia induced by bleeding, inoculation with tubercle bacilli did not prevent blood regeneration which appeared to proceed *pari passu* in inoculated and uninoculated rabbits. Whether the results might have been different had we succeeded in keeping the rabbits for prolonged periods at a low haemoglobin percentage is a moot point. Whipple and his coworkers (1925) and Hahn and Whipple (1936) found that the relative values of different foodstuffs and iron preparations on blood regeneration in dogs could be investigated only when their dogs were kept for months with their haemoglobin percentage reduced to one-half or one-third of its original value by repeated large bleedings so as to exhaust the iron reserve. We could not continue repeated large bleedings for months in rabbits as their accessible veins become thrombosed after a time and further bleedings become impossible. We must conclude that in our experiments we had not exhausted the inherent reserves of the rabbit for blood regeneration. That such reserves exist would appear from the work of Whipple and his colleagues (1920) who noted that blood regeneration in dogs after the first bleeding was sometimes extraordinarily rapid even on a diet of bread and milk. When the same dog was bled a second time, however, this rapid regeneration did not take place on the same diet.

CONCLUSIONS

1. Immediately after bleeding there was in 75 per cent of cases a marked fall in the pH of the healthy rabbit's blood. This fall was in no way connected with the amount of blood withdrawn but was related to the state of the veins after the bleeding. In 25 per cent in which there was no change in the local condition of the veins, no alteration in pH was noted.

2. This fall in pH was temporary. On the day following the bleeding when the rabbit was, as a rule, very quiet, the pH was higher than before. On subsequent examinations the pH varied as with normal unbled rabbits.

3. The pH value bore no relationship to the haemoglobin content of the blood, before or after bleeding.

4. Infection of rabbits with tubercle bacilli, whether of human or bovine strain, appeared to have no effect on the pH of the blood.

5. Blood pigment regeneration was complete in three weeks after a single large bleeding, at which 45 per cent of the total circulating blood volume was withdrawn.

6. Infection with *B. tuberculosis* appeared to have no immediate paralyzing effect on the regenerative powers of the haemopoietic tissues of the rabbit after haemorrhage.

7. The anaemia certainly did not break down the rabbit's known resistance to the human strain of the tubercle bacillus.

8. Where the infecting agent was a bovine strain the autopsy findings showed somewhat more advanced disease in the majority of the bled rabbits as compared with the unbled controls, but the difference was not sufficiently great to make definite deductions therefrom. The inherent difficulty of the experiments was the inability to maintain the anaemia for a sufficiently long period.

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THE PATHOGENESIS OF TUBERCULOSIS IN CHILDREN[1,2]

HENRY STUART WILLIS

Until a few years ago tuberculosis in children was thought, at least in America, to be identical with the disease in adults and to be rare except for the fatal miliary and meningitic types in infants. The work of Hempelmann (1), Chadwick (2), Austrian (3), Bushnell (4), Happ and Casparis (5), Myers (6) and a few others focused attention upon the fact that the disease in children has numerous characteristics which set it off sharply from tuberculosis in older people. These studies have yielded some astonishing facts in respect to the incidence, the evolution and the termination of this disease in children and have given us a new view of the disease which we now recognize as being characterized by (*1*) a relatively large amount of disease anatomically, associated with involvement of the tracheobronchial lymph nodes; (*2*) relatively slight symptoms in the main; and (*3*) a marked tendency to heal in older children, a very high fatality rate in those under two years of age.

Any discussion of tuberculosis in children should recognize that the subject embraces two distinct types of disease, each with its characteristic course and prognosis. One type is the progressive, often rapidly fatal disease in infants or very young children, which is found mostly in those having intimate and extensive exposure. Frequently it passes unremittingly from first infection to lethal experience. Characteristically it involves the lymph nodes at the root and large areas of the lung with extensive caseation and cavitation, and often it terminates in widespread generalized disease, miliary tuberculosis or tuberculous meningitis. Asserson (7) dealt largely with this type when she found that 82 per cent of children ill and in hospitals with clinical tuberculosis died of tuberculosis if their disease was contracted before the end of the second year of life. In the same tenor Blacklock (8) reported a very high death rate among such children and attributed the seriousness of

[1] Read before a meeting of The Mississippi Valley Sanatorium Association, Dayton, Ohio, September 24, 1937.

[2] From the Wm. H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Michigan.

the issue to excessive and repeated infection in the intimate contacts of early life which allows the infant to become saturated with tuberculosis that outstrips all barriers. Of Brailey's (9) children who acquired tuberculin reaction before the age of six months, 78 per cent died within the first five years of observation. In Rosenberg and Kereszturi's (10) 348 children contracting tuberculous infection in the first five years of life, the total death rate from tuberculosis was 9 per cent. None who had been infected after one and one-half years of age died during a long observation period, but 40 per cent of those contracting infection by the age of three months died before they reached age one. The appalling human experiment at Lübeck, in which 247 children were infected by mistake with proved virulent tubercle bacilli (11) instead of the apparently harmless BCG, offers gruesome evidence that infants and small children are highly susceptible to tuberculosis.

The other type is more or less self-limited and, to a considerable extent, self-healing. It presents itself chiefly as an affection involving the lung and the tracheobronchial lymph nodes, producing often only mild symptoms and, on the average, undergoing satisfactory healing. Its subjects are somewhat liable to exacerbation of the lesion, even years after it has become calcified, and they are not infrequently the victims of reinfection from external sources. It is seen characteristically in children beyond the period of infancy, and its *relative* benignity rests undoubtedly upon other factors than age,—especially that of repeated dosage. It is regarded as "first infection tuberculosis" to which the term "childhood type" has been applied widely.

It is believed that such grouping is more than a division of convenience; that it rests firmly on practical observation. Whether both groups be called first infection type or childhood type, their course and effect are decidedly different, although they are obviously facets of the same affection. For the present purpose the first group may be dispensed with by saying that it represents a most serious disease, with a terrific death toll and one which resembles closely the tuberculosis produced in experimental animals by large doses of tubercle bacilli. Such children seem unable, by virtue of repeated infections, to develop typical childhood type or primary infection tuberculosis. These two terms will be used synonymously in this paper.[3]

[3] The term childhood type is now well established. Its proponents recognized its shortcomings at the advent of its use but could find no satisfactory substitute. As time has passed, the reasonable objections have increased rather than decreased, and this despite the fact that the term has become ever more closely linked to the clinical entity presented by the

We will discuss this condition in some of its contrasting points with ordinary tuberculosis in adults. It has been ten years since a committee of the National Tuberculosis Association suggested the terms "childhood type" and "adult type" to indicate whether the disease represented so called first infection or reinfection. Although the terms are applicable to tuberculosis in the chest only and are in need of revision, they have come into wide use and have come to imply a great deal prognostically. By way of reorienting ourselves let it suffice to recall a few of the contrasts between first infection and reinfection tuberculosis. All of us know that, excepting the group just mentioned, the first infection type is frequently without the conspicuous symptoms which attend the average reinfection type case; that the childhood pulmonary lesion is likely to be disproportionately large anatomically; that it almost invariably involves the tracheobronchial lymph nodes, is exudative in quality and presents the macroscopical and microscopical appearance of tuberculous (gelatinous) pneumonia; that it is but slightly fibrous in character; that it resolves at an almost regular and predictable rate when complications do not appear and that the prognosis is good.

Factors that determine pathological response: Numerous potential factors may modify the characteristics assumed by tuberculous disease in children and in adults. The child's environmental influences differ from those of the adult in several ways. A few of the more important of these will be considered briefly:

1. *Age:* Whether age of tissues determines tissue response to the tubercle bacillus is moot. Some experimental data suggest the truth of this postulate. However, it is highly probable that opportunity for infection in infancy and early childhood determines the fate of those infected, more than age itself does. The infant is greatly restricted as to the number of its human contacts, and it associates frequently with them (members of the family, nurse, etc.). If it becomes infected, it probably does so from a source near at hand and one which infects it often. From this point of view it is in reality dose rather than age *per se* that is most important in the development of tuberculosis in infants and young children.

2. *Dose:* But little is known of the numbers of tubercle bacilli which are requisite for infection and disease in man. Experimentally it has

"average" case of tuberculosis in children above the infant age. The objections to its use are well known and do not need review. It is to be hoped that more definitive nomenclature can be devised. It is known that the Committee on Diagnostic Standards of the National Tuberculosis Association is wrestling with the question at this time.

been demonstrated that a very few may establish disease. For instance, Schwabacher and Wilson (12) have shown recently that "the minimal infective dose is probably rather over 10 living organisms." Also, experiments show that variations in volume and time relationship of doses determine the severity, rate of development, the course and eventual result. Clinically, the effect of frequent small doses is manifested in the so called haematogenous pulmonary tuberculosis in which a large total number of bacilli are fed into the lung—at least a large total number of small foci develop—but they appear to arrive in small deliveries so that the body takes relatively good care of them. Yet so called "massive dose" fails to explain the entire issue, because numerous children escape infection and disease after heavy and repeated exposure.

3. *Virulence of strain:* The virulence of strains varies somewhat. Certain strains isolated from the skin and peripheral parts of the body tend to have reduced virulence. But as a general rule, the virulence of tubercle bacilli remains constant and is high.

May virulence of the tubercle bacillus then determine the response of the child or the adult to its invasion? It seems altogether unlikely. In a household with open tuberculosis the same strain (presumably) infects several members. Yet one child will die from his acquired tuberculosis, another will become ill and recover, a third may become tuberculin-positive but not clinically diseased, and a fourth may escape infection entirely. Such variations cannot be put down to virulence of the strain. Much more likely the variations in numbers of bacilli and in the frequency and manner of their intake are, along with personal or individual variation in response, the determining factors.

4. *Diseases of childhood:* In the past there has been general consensus that the infectious diseases of childhood, especially measles, exert a baneful influence on tuberculous infection or tuberculous disease in children. Recently Nalbant (13) has questioned this and has supported his criticism with a considerable body of fact. For instance, in 147 children (in a tuberculosis sanatorium) who developed one or another of the common acute infectious diseases in the course of childhood tuberculosis, the incidence of relapse was no greater than among the larger number of children who were in the institution concurrently but who did not develop such intercurrent diseases. In another recent study, on the other hand, Mitchell (14) observed a distinct tendency for tuberculosis to undergo exacerbation in sanatorium children who went through an epidemic of streptococcic sore throat. Fourteen of 89 children in the series thus studied experienced increase in their tuberculosis. At

least it must be admitted that the infectious diseases of childhood do constitute an environmental factor that is usually absent in adults.

5. *Anatomical differences in child and adult:* Anatomists have stressed certain differences in the anatomy and function of the lung in the child and adult. In the former the lymphatic channels are relatively large and open; they lack the scarring, narrowing and tortuosity of those in the adult lung which come as a result of disease or inhalation of dust; only scanty amounts of lymphoid tissue act as dampers or filters through which the lymph flows, so that foreign material, particulate matter, tubercle bacilli, etc. are carried more readily to the lymph nodes at the root (Miller (15)). Such facts may have some influence upon the prominence of the tracheobronchial lymph nodes in tuberculosis of children.

6. *Influence of previous tuberculous infection:* This question will bear more or less extended analysis, for on it is to rest the burden of the contention to be presented. It may be approached from two points of view: first, whether the allergic state existing in the child and adult at the time the infection is acquired affects the issue differently in the two groups, and, second, whether immunity exists with childhood type infection.

Previous infection implies allergy or changed reaction. It means the response to the tubercle bacillus is more prompt, acute and inflammatory than it is in first infection. It provides the basis for all the more acute phenomena associated with tuberculosis—tuberculous pneumonia, pleurisy with effusion, the collateral inflammation around the seat of tuberculosis in lung or lymph node, the stormy symptoms of any acute manifestation of tuberculosis and of the illness which follows overdose of tuberculin.

Allergy fluctuates. It is high early after infection, and it tends to wane when infection has been established a long time. For this reason children who have tuberculous infection react in general more vigorously to tuberculin than adults do, and in this fact may lie much of the genius of childhood type disease, because reaction to tuberculin and to tubercle bacilli is basically similar. Allergy has been shown to affect all tissues of the body. But why should pulmonary lesions, size for size, be less menacing in childhood type than in adult type tuberculosis, which is generally granted as being true? This fact may be and very likely is linked up with the interplay between the degree of allergy and the size of the infecting dose. The degree of the reaction varies with the size of the dose and the height of the allergy. Low allergy and small dose

lead to trifling response; low allergy and large dose to moderate or extensive reaction and potential tissue destruction and spread of disease. High allergy and small dose cause moderate or moderately severe reaction with extensive collateral inflammation (consolidation) around the focus and more or less tissue injury; high allergy and large dose produce severe reaction and extensive tissue damage. It is probable that the high allergy and small dose combination corresponds to the state of most children because of recency of infection (high allergy) and because the average dose is small (?)—since about one-half of tuberculous children have no history of contact.

In the light of these several factors may we not properly ask what underlying pathological principles are involved? In seeking a rational answer, let us look into definitions for a moment. In the literature the terms primary infection, first infection, childhood type, Ghon focus, primary complex are used more or less synonomously. But is this correct? Primary infection indicates actually the response to first entrance of tubercle bacilli into the body; childhood type is raiment for a series of multiform reactions of the child to tubercle bacilli in lung or tracheobronchial lymph node. The term "Ghon focus" is applied to the residual calcium depot at the site of earlier tuberculosis in the lung or tracheobronchial lymph node and "primary complex" signifies the primary parenchymal and lymph node focus as a process from start to finish. "Primary infection," "first infection," or "childhood type" indicate disease. "Complex," "focus" stand as pathological or anatomical entities. We may conceive of *clinical* first infections as the composite episode from intake of bacilli, through parenchymal and lymph node disease to the final calcified focus. This, conventionally called the primary complex, may be regarded as an entity in the child's life. However, when this total picture is broken down into several component parts and analyzed pathologically, some interesting features present themselves. In the first place the pathologist sees a discrepancy in the term "first infection" when applied to the gamut known as the "primary complex." He knows that the initial reaction to the tubercle bacillus is relatively small, inconspicuous, and of slow evolution; that the type of reaction is different after the animal or child has had his infection for even two, three, or a few weeks, because the bearer becomes allergic. He is convinced that the body's newly acquired allergy begins to show itself at the existing lesion which it converts into an inflammatory area that becomes thereby much larger in extent than the original, and be-

comes the lesion that is detectable on the X-ray film of the lungs. Pathologically such reaction has the characteristics of reinfection tuberculosis.

He is aware, further, that there is a great difference in what happens to the tubercle bacilli that enter the lungs of a noninfected and the lungs of an infected child. In the one they spread with the greatest of ease and in the other they get away from the point of location with great difficulty. It is demonstrated conclusively that tubercle bacilli spread with great facility along the drainage routes in the uninfected animal; in fact, that they get under transport within the first few hours of inoculation and that they travel to the lymph nodes at converging points in the drainage system. Experiments show that some of them invariably leave the point of inoculation within three hours of their implantation and travel a distance as great as two inches in twenty-four hours, to reach regional lymph nodes. Of equal significance is the fact that in the allergic animal, migration of tubercle bacilli from the point of inoculation progresses very slowly.

It has been shown that this rapid passage of tubercle bacilli is the norm for noninfected animals. Illustrating this prinicple is the work of Opie (16) which demonstrated that protein is fixed at the point of injection in sensitized animals whereas it diffuses rapidly in nonsensitized ones. From this point of view, then, much of the issue of childhood tuberculosis turns on what happens in those few days or weeks which elapse between implantation of bacilli in the lungs and the development of allergy. Passing through the relatively large, open lymphatics, the bacilli have a journey that is relatively unimpeded by lymphoid tissue and reach the lymph nodes at the root of the lungs where they are held for the most part and where they set up disease. But, much more important, they pass through human tissues that are not allergic and that thus offer no added specific barrier, chemical or physical, to their transportation. In these first days actually many bacilli may pass on to the tracheobronchial lymph nodes, possibly more than remain *in situ*. Witness Blacklock's (8) work which revealed lesions in tracheobronchial lymph nodes in almost every single case of parenchymal disease and which showed that the disease in the lymph nodes appeared usually to be the same age as that in the lung. In this he confirmed the observation made by Parrot (17) in 1876, by Küss (18) in 1898 and by Ghon (19) in 1915.[4] Similarly, Ghon (19) found only one case in 170 of child-

[4] Fried (Arch. Path., 1936, *22*, 829) has given a brief and very clear-cut review of the primary complex.

hood type pulmonary tuberculosis without associated tuberculosis in the regional lymph nodes.

Tubercle bacilli have been inoculated subcutaneously into guinea pigs and recovered from the tracheobronchial lymph nodes at the same time and occasionally earlier than they can be found in the lungs, through which organ ordinarily they would have to pass before reaching these nodes. In almost exact keeping with this observation of Krause (20), Allen (21) has recently determined by serial roentgenological study, that children with tuberculous disease of the tracheobronchial lymph nodes have associated pulmonary lesions that may be inconspicuous until calcification has occurred; in other words, lesion in the regional lymph nodes is often more extensive and more prominent than its parent lesion in the lung.

One deduction from this must be that many, perhaps most, of the bacilli originally brought to the parent focus are transported to the root. Such an occurrence would explain the extensive disease at the root and also, by the fewness of the bacilli, the relative scarcity of caseation in the pulmonary lesion.

But is there proof that drainage is less facile in the adult or in adult type disease? By inference and analogy such a deduction seems logical and justifiable. Tubercle bacilli do move very slowly and haltingly through the tissues of the allergic animal, as related above. Tuberculosis tends to be localized to a given organ or part of an organ in the adult type. Blacklock (8) could find tuberculosis in the lymph nodes that were regional to the area of the lung involved in primary lesion but was able to establish no such association or sequential relationship between secondary pulmonary foci (adult lesion) and disease in these nodes.

Can one then not conclude that the failure of tubercle bacilli to be carried away from the lung contributes to the seriousness of the tuberculosis concerned. Collateral evidence may be had in the work on silicosis in which the fibrosis of lung and lymphatic system traps or fixes tubercle bacilli which reach the organ and holds them there. In the silicotic lung, infection remains in the parenchyma and progresses locally because the normal drainage of the healthy lung no longer avails. In the person infected with tuberculosis, tubercle bacilli which reach the lung remain in the parenchyma and progress locally because the chemical or physical properties of allergy fix them there. If spread takes place in adult disease, it is relatively gross and occurs in remote parts of the body through the blood-stream or through the bronchi to other portions

of the lung. It rarely spreads to the tracheobronchial lymph nodes as it does in childhood type. The focus in the lung is rarely drained of its inciting agent as it is in childhood type.

So much for the physical and chemical properties of allergy that lead to fixation of bacilli at the point of introduction. But what of the immunity that supposedly attends infection? It is impossible at this time to discuss immunity, with its many facets, the many faults in our knowledge concerning it, the many theories postulated to explain it. Suffice it to call attention to the fact that man appears to possess a considerable degree of immunity to tuberculosis. How else explain the marked tendency of the disease to heal! Sixty per cent of us become infected with the tubercle bacillus and about one per cent of us develop clinical tuberculosis. Many who react to tuberculin—the adult in contact with disease in the home, the physician, nurse or attendant in the sanatorium or hospital—almost certainly meet tubercle bacilli not once but many times in a lifetime, yet remain free from clinical tuberculosis. Many of the one per cent who have the disease do not die from it although those who do come to attention need all that medical science can give in the way of hospital care and collapse treatment.

Whether such resistance or immunity is specific and the result of previous infection cannot be stated, for no unequivocal proof exists that previous tuberculous infection in human beings confers immunity. Although no such proof can be demonstrated in man, a very extensive literature shows the undoubted fact that it does so in experimental animals. The work of Koch (22), Trudeau (23), Römer (24), Baldwin (25), Krause (26) and many others attests this fact over and over. The clinical observation of Marfan (27), in 1886, that "scrophulous" patients never develop consumption, although not without many exceptions, represents opinion based on long experience; that is, infection in cervical lymph nodes tends to protect against subsequent infection in the lungs. Numerous workers, Rich and McCordock (28) among them, feel that the tissues of the infected animal (or man) offer soil unfavorable to the growth of tubercle bacilli.

At best specific immunity is but relative and partial. While it may operate adequately in many cases, the open cavity with its threat of bronchogenic spread, various strains and nonspecific factors may easily outstrip specific protection and lead to disaster. Who can say that our death rate might not be much higher were infection not so widespread.

So immunity to tuberculosis is a relative and complicated affair which

is subject to many influences. Until we can learn many more facts than are now known about immune phenomena, type of reaction to first and subsequent infection, the intensity of exposure, the degree and type of residual disease in those having had childhood type, we are unable to arrive dogmatically at conclusions as to protection from first infection, though this seems highly probable, and certainly we cannot, as some have done, assume blandly that first infection predisposes to adult type of disease. The fact that tuberculosis is prone to heal suggests strongly the operation of resistance or immunity.

In conclusion it may be said that an effort has been made to state the issue in terms of dynamic rather than cellular pathology and that many more questions are raised in this discussion than are answered by it. Most of the ideas are old ideas restated; some are theoretical and without factual support. They are presented, however, as review and for purposes of reflection and discussion. May they serve these ends.

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THE INFLUENCE OF SILICA ON THE NATURAL AND ACQUIRED RESISTANCE TO THE TUBERCLE BACILLUS[1]

ARTHUR J. VORWALD AND ANTHONY B. DELAHANT

All statistical studies of silicotics have shown an extraordinary incidence of tuberculosis. This has been ably demonstrated by the British authorities and their colleagues in South Africa. Evidence in this country, both in the clinical and pathological aspects, is equally convincing. Lanza and Vane (1), in analyzing the incidence of tuberculosis among silicotics of various trade groups, found the mortality from pulmonary tuberculosis about three times that in the general population. Russell and his coworkers (2) discovered a high incidence of tuberculosis among granite cutters in Barre, Vermont. Similar observations have been made by Pope and Zacks (3) for the State of Massachusetts.

Studies by the Saranac Laboratory are significant in this regard. A survey made in 1930 of the male and female population of Ottowa County in the Tri-State mining district of Southwestern Oklahoma disclosed a tuberculosis death rate of 241.3 per 100,000, whereas that for the entire state was only 39.9. In groups of iron ore miners with silicosis the trend is such as to indicate a morbidity rate of tuberculosis much higher than that in the nonmining population. In 167 pathological specimens of silicotic lungs of persons employed in various industries, 65 per cent revealed the presence of tuberculosis.

From these observations it becomes evident that silica, in some way, has a specific aetiological relationship to tuberculosis. The nature of this relationship, however, has not been satisfactorily explained. Discussion concerning it usually involves a consideration of two exceedingly complex questions: first, the influence of silica on the growth and virulence of the tubercle bacillus; and second, the influence of silica on the tissue resistance to the tubercle bacillus.

There is experimental evidence to support the view that silica enhances the growth of the tubercle bacillus (4, 5, 6). Not all laboratory

[1] From the Saranac Laboratory for the Study of Tuberculosis of The Edward L. Trudeau Foundation, Saranac Lake, New York.

investigations in this regard have been equally significant. Repeated attempts (7) such as by the addition of particulate silica, soluble silica, abdominal fluid from guinea pigs that has formed in response to intraperitoneal injection of silica and necrotic material from early silicotic lesions, to artificial culture media have not demonstrated such an effect.

Convincing proof is still lacking that increased growth of the tubercle bacillus occurs in advanced silico-tuberculous lesions from human subjects. Acid-fast bacilli are often more difficult to find in such lesions than in those of simple tuberculosis and in many instances their presence can be verified only after repeated guinea-pig inoculation. Such procedure has failed to show any greater virulence of these microörganisms than those isolated from lesions of uncomplicated phthisis. With reference to this it should be stated that experiments thus far completed in the Saranac Laboratory (8) have elicited no change in the microörganisms recovered from silico-tuberculous tissues of animals.

At the present time it appears that the mechanism responsible for the high incidence of tuberculosis among silicotics is associated with a decrease in the tissue resistance of the host to the bacillus. For purposes of clarification "resistance" is used to indicate the ability of the tissues to combat the infecting bacilli. When resistance is low the bacilli quickly gain the upper hand and give rise to widespread lesions with extensive tissue destruction. In such cases the tissue or host is often referred to as "susceptible" to the infectious agent. When the resistance is high the disease is only slowly progressive, remains stationary or completely resolves.

In an attempt to explain this mechanism a number of experiments are reported herewith. They were designed to study the influence of silica on the natural and the acquired resistance of animal tissues to infection with the tubercle bacillus.

NATURAL RESISTANCE

Two experimental methods may be employed to test natural resistance. An attenuated microörganism may be used as the infecting agent in a species of animal commonly susceptible to more virulent types of bacilli, or a virulent microörganism may be used to infect a species highly resistant to tuberculosis.

In the first method a strain of tubercle bacilli known as R1 has been consistently employed in this laboratory. This strain was originally

isolated from the lung of a human case of pulmonary tuberculosis. It is now in its forty-seventh year of cultivation. During this time it has lost its virulence so that the injection of moderate doses into normal guinea pigs now produces only isolated caseous tubercles. These lesions tend to heal by resolution and ultimately disappear. In silicotic animals, on the other hand, the inhalation of the same microörganisms has a very different effect. Such animals invariably develop chronic progressive disease and die in about one year's time (9). While these results have consistently shown such effect, the inhalation method cannot be controlled on a quantitative basis. To accomplish this result injection methods must be employed. Two experiments were therefore designed to infect guinea pigs with a known amount of microörganisms from the same culture.

Intraperitoneal Injection of Dust Plus Avirulent Tubercle Bacilli into Normal Guinea Pigs

A uniform suspension containing 0.2 gm. of finely ground dust and 2 mg. of triturated strain R1 bacilli was injected into the abdominal cavity of a series of guinea pigs. One series of four pigs received a pure free crystalline silica, as quartz. Another series was injected with granite dust and a final one with the silicate feldspar.

These three dusts were selected because they exemplify silica in its free form, in a mixture composed of free and combined forms, and a pure combined form. Quartz is a pure crystalline variety with 100 per cent total silica all of which is in a free state. Granite is a mixture of crystalline minerals of which 35 per cent is free quartz and the remainder is composed chiefly of the silicates feldspar and mica. Feldspar is a crystalline silicate with 65 per cent total silica all of which is combined. The use of these three forms is quite important because of the present day views that only uncombined or "free" silica causes silicosis; that the presence of other minerals tends to modify the action of the free silica; and that the silicates (combinations of silica with bases), with the exception of asbestos, cause little or no damage to the pulmonary tissue and therefore do not influence a bacillary infection.

Infection control animals were not introduced into the experiment. Ordinarily, intraperitoneal injection of R1 in this amount causes a self limited reaction localized to the peritoneum with no extension to the viscera. This has been repeatedly verified in this laboratory.

The guinea pigs were sacrificed at varying intervals after infection,

10, 24, 29 and 114 days respectively. At all periods the infected lesions were considerably larger than those in the noninfected dust control group. The quartz plus R1 suspension produced larger lesions than did either the granite plus R1 or the feldspar plus R1. The latter were usually the smallest of the three. Microscopical differentiation between the reactions could not be made at the early periods, for all lesions exhibited wide central areas of polymorphonuclear leucocytes surrounded by mononuclear cells. By the 114th day there was a marked qualitative difference in the response to the various combinations. The infected feldspar lesions revealed only small necrotic centres with widely scattered leucocytes and deposits of calcium salts surrounded by thick zones of mononuclear cells and fibrous tissue. The tuberculous quartz and granite reactions were still acute with large central foci of leucocytes and necrosis.

The infected dust lesions were examined for tubercle bacilli. There was very little to differentiate between the number and character of the bacilli found at the early periods. At the final period acid-fast microorganisms were more numerous in the quartz than in the granite lesions and could not be demonstrated in the feldspar reactions.

Although the spleens in these animals showed no specific change characteristic for any of the groups, conspicuous differences were observed in other organs, namely, in the lung and liver. Those in the feldspar group, at the early periods, disclosed a few widely scattered small tubercles. By the 114th day both organs were free of disease. At the same period the granite pigs revealed few tubercles in the liver but none in the lung, whereas the quartz animals showed numerous large tubercles in both organs.

Summary and comment: The observations on the effects of quartz, granite and feldspar dusts substantiated the generally recognized opinion as to their relative capacities to excite reaction in the tissues. It was proportional to their free silica content. The same may be said of their influence upon infection with attenuated tubercle bacilli. The quartz caused the infection to become progressive and to spread to other organs. Granite, with only 35 per cent free silica, caused considerable local proliferation of the bacilli, but not enough were shed continuously into the blood-stream to maintain reactions in remote organs for very long. Feldspar caused only a temporary local effect upon the growth of the microörganisms, a few metastasized to other organs and formed

temporary reactions that soon subsided. This behavior approximated that in the control animals injected with bacilli alone.

Intravenous Injection of Virulent Tubercle Bacilli into Silicotic White Rats

The second method used to test the action of silica on the natural resistance of a tissue to infection employed a species of animals highly resistant to virulent tubercle bacilli. Rats were most suitable

TABLE 1

White rats with inhalation of dust and intravenous injection of tubercle bacilli

TYPE OF EXPOSURE	DUST CONTROL	PERIOD OF INFECTION		
		20 days	44 days	70 days
	rats	*rats*	*rats*	*rats*
Quartz (240 days)	1, 2, 3	23	24	25
Chert (240 days)	8, 9	33	34	35
Gypsum (240 days)	15, 16	45	46	47
Gypsum + quartz (240 days)	19, 20	51	52	53
Infection control		57	58	59, 60, 61
		22 days	42 days	67 days
Quartz (330 days)	4, 5, 6	26, 28	27	
Chert (240 days)	10, 11	36	37	38
Hematite (365 days)	12, 13	39	40	41
Gypsum (330 days)	17, 18	48	49	50
Gypsum + quartz (365 days)	21, 22	54	55	56
Infection control		62	63	64
		31 days	48 days	83 days
Quartz (369 days)	7	30	31	32
Hematite (369 days)	14	42	43	44
Infection control		65	66	67

animals for this purpose because they also show a marked tendency to develop silicotic lesions in the lung. After six to eight months' inhalation of quartz they exhibit pulmonary nodules of mature fibrous tissue.

Groups of rats were made to inhale one of the following types of dust for prolonged periods varying from 240 to 569 days: quartz, free crystalline silica; ferruginous chert, a natural mixture of equal parts of iron oxide and free cryptocrystalline silica (chalcedony); hematite, iron oxide contaminated with 6 per cent silica in the form of quartz; and gypsum, a calcium sulphate. Another group of animals exposed to an artificial

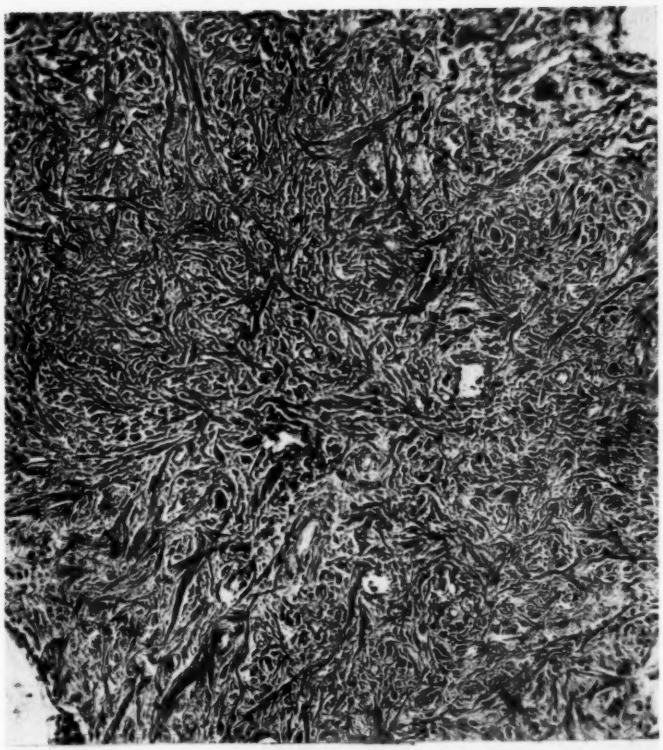

Fig. 1

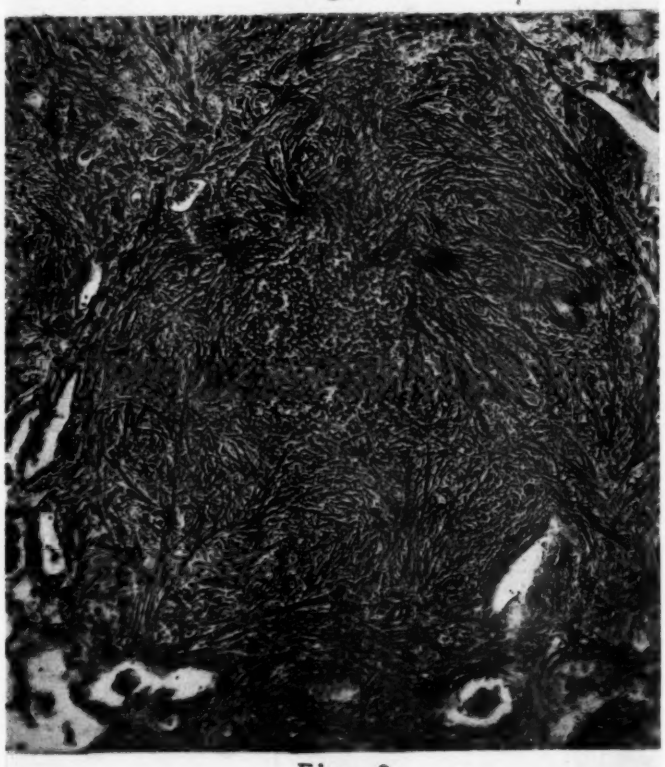

Fig. 2

mixture of equal parts of gypsum and quartz was also introduced into the experiment. This was done to elicit any modifying effect that gypsum might have on the reaction between quartz and tubercle bacilli in the tissues. After exposure, the rats were removed from the dusting house and infected intravenously with 5 mg. of virulent tubercle bacilli, strain H63. They were sacrificed at varying intervals after infection. Reference may be made to table 1 for information specific to each animal in this experiment.

The dust control animals (numbers 1 to 22) showed varying amounts of pigment within the pulmonary parenchyma. Those exposed to pure quartz dust (1 to 7) responded with characteristic nodules of hyaline fibrotic tissue (figure 1). The animals that had inhaled the mixture of gypsum and quartz dust (19 to 22) ultimately developed the same result but at a much slower rate. These nodules exhibited widely spaced blood capillaries and scattered small foci of lymphocytes and mononuclear cells. Polynuclear infiltration and foci of necrosis were absent in mature lesions. In the alveolar spaces about the nodules there were isolated large mononuclear phagocytes, the majority of which usually contained small dust particles. Two types of these cells were generally distinguishable: a histiocyte type with basophilic cytoplasm of uniform density and eccentric nuclei rich in chromatin; and a clasmatocyte with foamy acidophilic cytoplasm and nuclei poor in chromatin. The former were in the majority and had often fused into large giant cells so characteristic in all tissue reactions to silica.

The ferruginous chert dust, although it contained about 50 per cent free silica, failed to produce any fibrosis in the lungs of these animals (8 to 11). At first this was thought to be due to a protective action of the iron component taking place in the tissues. Later analyses of the dust suspended in the air revealed that there was only about one-fifth as much silica in the atmosphere as was present in the original dust placed in the hopper. Subsequently it has been discovered that many nonsiliceous particles associated with silica in the atmosphere tend to reduce the

FIG. 1. Silicotic nodule in the lung of a white rat after one year three months' inhalation of pure quartz dust. The nodule is composed of mature fibrotic tissue. × 115

FIG. 2. Silico-tuberculous nodule in the lung of a white rat after one year six months' inhalation of pure quartz dust and thirty-one days after intravenous tubercle bacilli. The centre of the nodule is necrotic and infiltrated with polymorphonuclear leucocytes. Such foci are rich in acid-fast bacilli. × 115

Fig. 3

Fig. 4

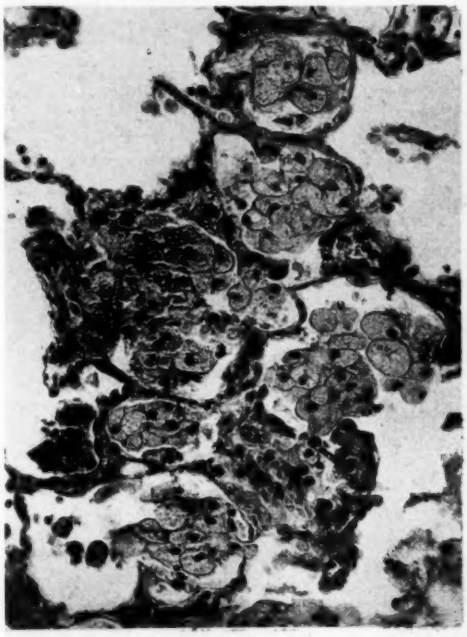

Fig. 5

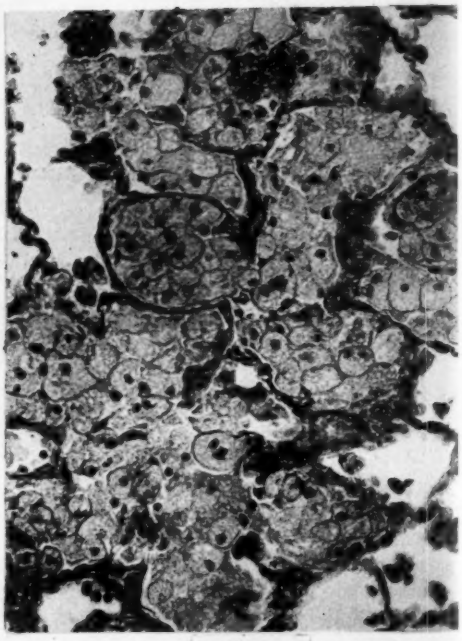

Fig. 6

amount of silica remaining in suspension. The 10 per cent silicon dioxide available in the chert experiment was only slightly in excess of that in the hematite series (7 per cent). Theoretically the tissue reactions caused by these two dusts should have been quite similar and as a matter of fact this was actually the case. The reactions to these dusts (8 to 14) can be summarized together. The dust particles, localized in large phagocytic cells mainly of the clasmatocyte type, were scattered throughout the alveolar spaces. In many instances, particularly with the 10 per cent silica chert, these cells tended to collect in focal areas. In and about such areas there was often a slight accumulation of lymphocytes and small mononuclear cells. Nowhere were such reactions accompanied by fibrosis. The gypsum dust alone (15 to 18) caused hardly any reaction. It was taken up by phagocytic cells of the clasmatocyte type that lay free within the alveolar spaces. It failed to induce a response other than might occur to any inert material foreign to the pulmonary tissue.

The infection control animals (57 to 67) developed a moderate increase in the number of large mononuclear phagocytes (figure 3) within the air spaces. These phagocytes, in contrast to those that responded in the quartz rats, were mainly large cells with distinct clear cut borders, foamy acidophilic cytoplasm and eccentric nuclei poor in chromatin. They were usually well defined having failed to fuse into giant cells or tubercles. For purposes of classification these have been called clasmatocyte types to distinguish them from other phagocytes of the histiocyte type that were also present. The latter forms were decidedly less numerous. They were generally smaller and possessed basophilic cytoplasm with eccentric nuclei rich in chromatin. In few instances they had coalesced into giant cells, but typical tubercle formation had not

FIG. 3. Rat lung eighty-three days after intravenous tubercle bacilli. The alveolar spaces contain numerous mononuclear phagocytes of the clasmatocytic type with large foamy cytoplasm and nuclei poor in chromatin. × 230.

FIG. 4. Rat lung after one year nine months' inhalation of quartz dust and eighty-three days after intravenous tubercle bacilli. The alveolar spaces about and between the silicotic nodules contain numerous stimulated mononuclear phagocytes of the histocyte type. They have fused into large masses. × 230

FIG. 5. Rat lung after eight months' inhalation of 10 per cent silica chert dust and sixty-seven days after intravenous tubercle bacilli. As in fig. 3 the alveolar spaces contain numerous mononuclear phagocytes of the clasmatocyte type. Many contain scattered dust particles. × 230

FIG. 6. Rat lung after eleven months' inhalation of gypsum dust and sixty-seven days after intravenous tubercle bacilli. Comment as in fig. 5. Dust particles are not seen. × 230

resulted. Acid-fast bacilli were about equally distributed in both types of cells. Most often they were found as single long forms and well beaded.

A comparison between the dusted animals infected with tubercle bacilli and those of the control groups revealed conspicuous differences. This was most pronounced in the tuberculous animals of the quartz (23 to 32) and the quartz plus gypsum (51 to 56) series. In the infected silicotic nodules (figure 2) produced by these dusts the centres of the nodules contained appreciable collections of polymorphonuclear leucocytes with large clumps of tubercle bacilli visible with low dry magnification. In uncomplicated nodules of simple silicosis (figure 1) central polynuclear accumulations were entirely absent. In the infection controls (figure 3) no nodules developed.

The alveolar spaces about and between the infected nodules revealed varying numbers of large mononuclear phagocytes. As in the dust control animals the histiocyte forms (figure 4) predominated. Again they had fused forming large alveolar masses that contained many small quartz particles easily visualized under the polarizing microscope. Acid-fast bacilli in branched forms and clumps were scattered throughout such masses.

The pulmonary reactions indicative of bacillary infection were not marked in animals of the chert (figure 5), the hematite and gypsum (figure 6) series. In general the tuberculous involvement was comparable to that in the infected control group.

The pathology in other organs was significant only in so far as it indicated evidence of tuberculous spread. This was best exemplified in the liver and spleen of each infected animal in the quartz and the quartz plus gypsum groups. These organs showed scattered tubercles that were consistently larger and more numerous than those in the infected control animals. Other organs presented no consistent indications of a difference in the response to bacillary infection.

Summary and comment: This experiment demonstrated that silica in the form of pure quartz lowered the natural resistance of the white rat to infection with virulent tubercle bacilli. This effect was proportional to the concentration of free silica in the tissues, for other forms of dust such as 10 per cent silica chert, 7 per cent silica hematite and nonsiliceous gypsum had no such effect. Several other observations are worthy of comment for they present a possible explanation of the

mechanisms involved. In the white rat silica called forth large numbers of phagocytic cells of the histiocyte type, while other dusts low in silica and the tubercle bacillus excited the formation of foamy clasmatocytes. Whether these cells were transitional forms of a common stem cell did not concern us here. The important fact was that rats responding with the former type became more susceptible to the infecting microörganisms, whereas when the response was clasmatocytic in type they maintained the usual resistance of the species to the tubercle bacillus. These observations have suggested the hypothesis that silica stimulates mononuclear phagocytes of the histiocyte type whose altered composition satisfies the metabolic requirements of the tubercle bacillus and favors progression of the disease.

ACQUIRED RESISTANCE

The customary experimental method of producing an increased resistance to an infectious process is by previous injection of a virus of that disease. In tuberculosis this is usually accomplished either by injecting heat-killed tubercle bacilli or microörganisms of attenuated virulence. This results in what is spoken of as "artificially acquired resistance."

A desirable method of performing such experiments would be to make them as comparable as possible to the course of human disease. Naturally, therefore one would like to produce a sensitizing but regressive tuberculous lesion in the lung, then subject the animal to the inhalation of silica and subsequently reinfect it by the inhalation method. This procedure, however, falls short of the desired results. In using dead bacilli for immunization the animal has lost its resistance by the time it has had sufficient exposure to silica dust. The sensitivity has disappeared and the increased tissue resistance can no longer be elicited. Live microörganisms cannot be used for silica stimulates the primary infection as long as viable bacilli remain in the lesion. This occurs regardless of how or where the primary infection is localized. If bacilli are injected subcutaneously, intratesticularly or into the groin of an experimental animal, lesions of endogenous origin occur in the lung. These in turn become reactivated by inhaled quartz particles before an artificial reinfection can be given. It is obvious that some other experimental method must be employed to study the influence of silica on acquired resistance to the tubercle bacillus.

Intratesticular Injection of Quartz Dust Plus Vaccine Followed by Subcutaneous Infection with Virulent Tubercle Bacilli in Guinea Pigs

A series of pigs were divided into two groups. Group 1 received three intratesticular injections totaling 6 mg. of heat-killed tubercle bacilli, strain H63, and 0.03 gm. of silica. Group 2 was injected similarly with heat-killed microörganisms alone. The testes were used in the hope that both the bacilli and the dust would be kept localized and thereby exert their maximum effect.

The animals of both groups were skin tested one month later with 0.1 cc. of 2 per cent Old Tuberculin. A third group of normal animals to be used subsequently as the infection controls was also introduced into the experiment at this time. The tuberculin test readings (table 2) indicate that there was generally more reaction to intracutaneous tuberculin in the vaccine plus quartz group. They also suggest that silica

TABLE 2

Skin hypersensitivity in guinea pigs immunized with tubercle bacillus vaccine plus quartz and vaccine alone

GROUP	ERYTHEMA	INDURATION	NECROSIS
	mm.	mm.	mm.
1. 12 pigs—Vaccine + quartz	17.3 × 17.5	14.2 × 14.6	9.1 × 9.6
2. 12 pigs—Vaccine alone	14.8 × 14.6	12.9 × 11.9	6.5 × 6.3
3. 12 pigs—Normal	0	0	0

when injected with dead tubercle bacilli augments the tissue sensitivity conferred by these bacilli.

All animals were infected intracutaneously with 0.001 mg. of virulent tubercle bacilli, strain H63. The intracutaneous site of infection was observed daily for the first nine days. In general the lesions that developed in the vaccine plus quartz group were slightly larger with more erythema, induration and necrosis that those of the remaining two groups. These observations again indicate that the animals injected with vaccine plus quartz developed a higher degree of skin sensitivity than those injected with vaccine alone.

During the first six weeks after infection, members of each group were killed. After this interval, however, the animals died at odd periods and a strict comparison of the disease present at definite time intervals could not be made. The maximum survival was about the same for the three groups. On terminating the experiment a comparison

between the groups revealed that the tuberculosis was generally more extensive in animals of the vaccine plus quartz group and least so in those of the vaccine group. The infection control group showed as much tuberculosis as the first group. Observations on the basis of splenic enlargement disclosed that 60 per cent in the control group, 55 per cent in the vaccine plus silica group and only 25 per cent in the vaccine group exceeded 2.5 cm. in maximum measurement.

Summary and comment: This experiment suggests that silica when injected with dead tubercle bacilli augments the tissue sensitivity conferred by such bacilli. This was best demonstrated by the skin hypersensitiveness to tuberculin and moderately so by the subcutaneous injection of virulent tubercle bacilli. This hypersensitivity, although a product of the combination of the two irritating agents, silica and dead tubercle bacilli, was nevertheless a specific result of the latter. It might be assumed that silica, since it is capable of exciting a nodular response in the tissues similar to that produced by the tubercle bacillus, also confers a sensitivity to the tissues of the body. We have never been able to demonstrate that such is the case. It is suggested that the inflammation excited by the combination of tubercle bacilli and silica may be responsible for a more active dissemination of sensitizing proteins.

In spite of this apparent increased sensitivity the animals in the vaccine plus quartz group showed no resistance to active infection, at least no more than did those in the infection control group. If the size of the spleens is used as an index of the amount of tuberculosis, the disease in the vaccine plus quartz group approximated that in the control nonvaccinated group and was decidedly more extensive than that in the vaccinated group.

Right Intratesticular Injection of Dust Plus Vaccine and Left Intratesticular Injection of Virulent Tubercle Bacilli in Guinea Pigs

It was now decided to inquire if this depression of resistance was specific for silica. The action of quartz was therefore compared with that of aluminum oxide, a nonsiliceous inert mineral. The method employed was slightly different from that in the preceding experiment. A suspension of 0.02 gm. of dust plus 5 mg. of heat-killed tubercle bacilli was injected into the right testis alone. One group received quartz dust combined with the vaccine, another aluminum oxide with vaccine and a third vaccine alone. Forty days after the immunizing inoculations the animals were tuberculin tested intracutaneously. All reacted very

strongly, but there was a slight tendency for the vaccine plus quartz group to be more positive. The next day the left testis in each animal of all groups was injected with 0.01 mg. of virulent tubercle bacilli, strain H63. The animals were sacrificed 6, 20, 34 and 46 days after infection.

Significant pathological changes occurred in both testes. In the vaccine plus dust series they were generally smaller and firmer than in those with dust or vaccine alone. When quartz dust was combined with the dead microörganisms destructive chronic inflammation resulted. Although less marked than with quartz, the reaction with aluminum oxide was sufficiently intense to indicate that dead tubercle bacilli combined with a dust, even one considered inactive, initiated an inflammatory response more severe than that produced by either the mineral or the bacilli alone. The evaluation of these results is best deferred until further observations have been completed. The left testes and

TABLE 3

Influence of silica on the acquired immunity of guinea pigs to the tubercle bacillus

GROUP	CHARACTER OF INJECTION		EXTENT OF DISEASE
	Right testis	Left testis	
1	Vaccine + SiO_2	Virulent tubercle bacilli	7.3+
2	Vaccine + Al_2O_3	Virulent tubercle bacilli	5.0+
3	Vaccine control	Virulent tubercle bacilli	4.5+

epididymes inoculated with virulent tubercle bacilli were generally larger than normal. All revealed definite evidence of infection.

At all periods there was a tendency for the disease to be more marked in the vaccine plus quartz group. Table 3 is presented to show the grouping of the animals, the character of the inoculum and the extent of the disease in other organs. The gross amount of tuberculosis in the lung, liver, spleen and lymph nodes was evaluated and designated by one to four plus signs. The sum of these readings was averaged for all animals in a single group. By this method the figure 16 would represent the maximum amount of tuberculosis possible in any of the groups. Reference to table 3 indicates that there was an appreciable difference in the extent of the disease in the various groups. The vaccine plus quartz group developed widespread disease and approximated one-half the possible maximum. The control vaccinated group developed less extensive disease. It was only slightly more than one-quarter the possible maximum. The vaccine plus aluminum oxide group, although

more resistant than the vaccine plus quartz, developed slightly more generalized disease than anticipated. The difference based upon groups of only four animals is probably not significant.

Summary and comment: These results may be compared with those in the preceding experiment. They again suggest, although not as strikingly, that silica when combined with a tubercle bacillus vaccine increases the skin hypersensitiveness to intracutaneous tuberculin. They also demonstrate that silica depresses the acquired resistance when it is localized in an area developing such immunity and that this effect is quite specific for silica.

GENERAL CONCLUSIONS

Experiment has demonstrated that silica depresses the native resistance of the guinea pig to attenuated tubercle bacilli and of the white rat to virulent types of these microörganisms.

Silica also inhibits the development of acquired resistance in guinea pigs when this irritant is confined to the tissue in which the immune bodies are being produced. In these early silicotic lesions evidences of decreased immunity are manifested in spite of an increased hypersensitiveness of the skin to tuberculin.

This adverse influence is specific for silica and is proportional to the concentration of the irritating substance. Dusts low in silica, such as 10 per cent silica chert, 7 per cent silica hematite, and nonsiliceous dusts, such as gypsum and aluminum oxide, have no such effect.

A possible explanation for this influence is that silica so alters monocytic cells that they furnish a more suitable medium for the growth of the tubercle bacillus. On the other hand, inhibitory substances normally present in such cells may be neutralized so that the bacillus is permitted to grow with unusual rapidity. At the present time only morphological evidences of cellular alteration have been discovered. The underlying chemical factors are completely unknown.

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PATHOLOGY OF THE SILICOTIC NODULE[1]

JOSEPH WALSH[2]

On account of proximity of the White Haven Sanatorium to the anthracite coal fields a large number of patients are admitted with anthracosilicosis, both with and without accompanying tuberculosis, and on account of its high mortality it is frequently seen at necropsy. The following pathological study pursued over the last twenty years on several hundred cases endeavors to show the manner of development of its principal feature, the fibroanthracosilicotic nodule.

Since it is almost universally granted that inhaled dust gains entrance to the lung tissue practically only from the terminal bronchioles and alveoli, our description begins after the arrival of the dust in these parts. Here we see it in cells known in consequence as dust cells which resemble the epithelioid cells and are generally considered to have the same origin. These cells containing innumerable dust granules (figure 1) are found in the lumen and in the walls of alveoli and terminal bronchioles and in lymph channels leading to intrapulmonary and hilar nodes.

As long as the lymph channels remain capable of removing the dust-containing cells, comparatively little happens locally, it is only after the nodes and their afferent lymphatics become blocked that the irritation of the silica dust leads to the visible development of fibrous tissue about them. This stagnation of dust and increase in fibrous tissue are evident at necropsy in the form of black lines extending toward the hilar nodes. In cross section these lines are visible as minute black specks. Roentgenographically they appear first as increased lung markings and only later as definite lines indicative of the process. The number of years required to reach this stage varies with the amount of dust inhaled, the amount reaching the fine ramifications of the respiratory tube, the amount of silica in the dust, and the susceptibility of the individual to the irritating action of the silica.

This obstruction of the lymph channels allows accumulation of the

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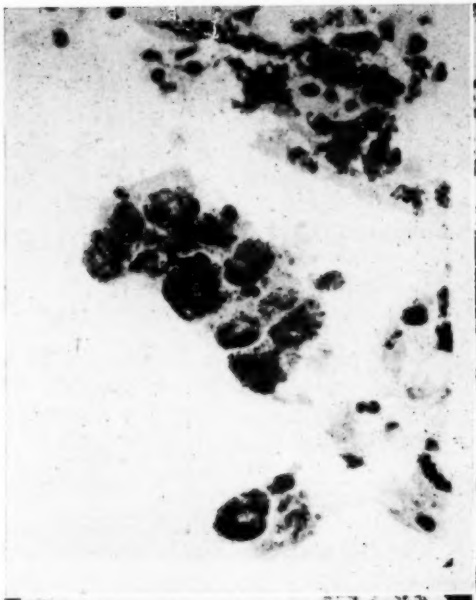
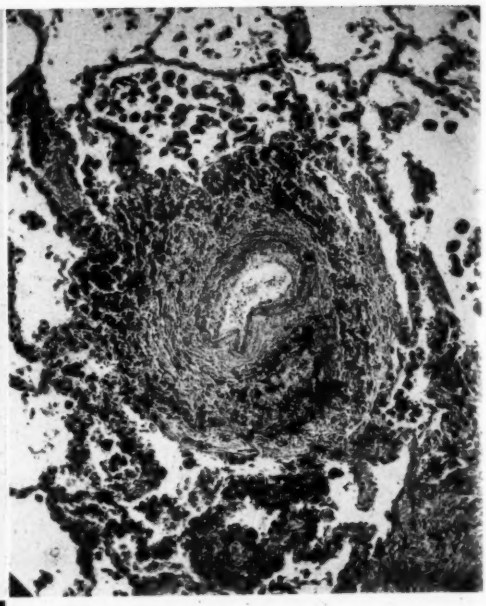


FIG. 1



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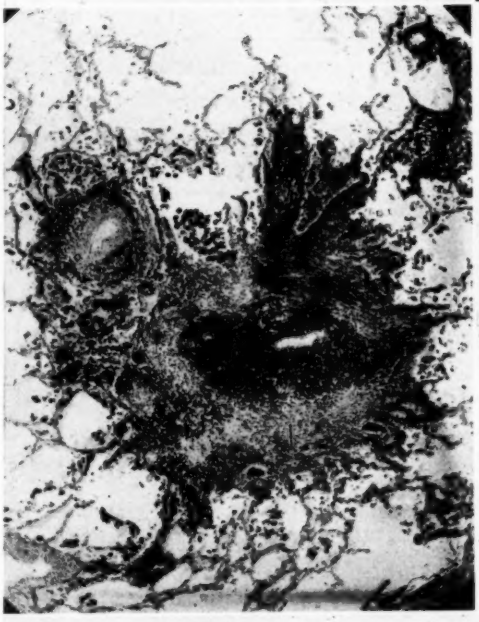

FIG. 3

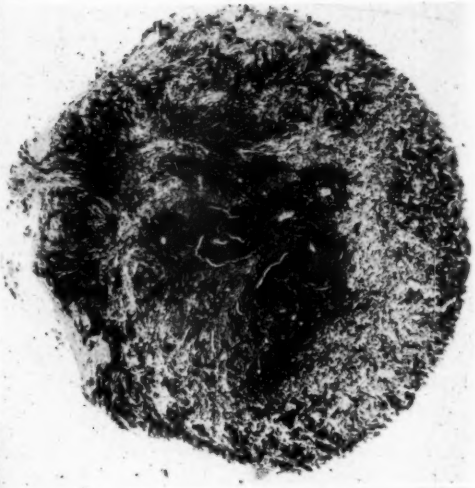

FIG. 4

FIG. 5

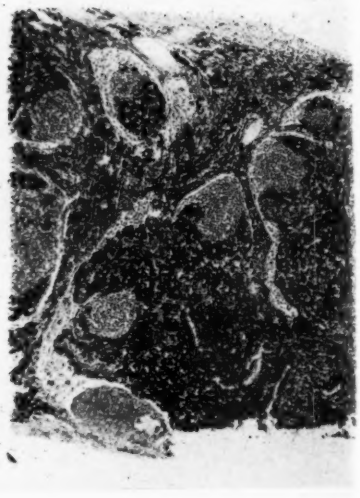

FIG. 6

dust cells in the lumen and the walls of alveoli and terminal bronchioles, as well as in intrapulmonary nodes, and leads to the development of fibrous tissue in these situations. This development in the walls of the alveoli is associated with destruction of the elastica, the consequent inability of further alveolar contraction, and the production of emphysema.

FIG. 1. Dust cells in an alveolus under the oil immersion lens (magnification about 600) in order to show how dust is carried and the innumerable microscopical granules in each cell. In anthracosilicosis the dust remains in cells until a late stage when the cells in the centre of the fibroanthracosilicotic nodule necrose and the dust runs together in heaps, and with no cushion of organic matter between the granules the knife grates on passing through. Philadelphia General Hospital Case No. 9805. Tuberculosis and anthracosis.

FIG. 2. Showing how the alveoli collapse about a blood vessel so as to form a fibroanthracosilicotic nodule. The alveoli become partially or entirely filled with dust cells; the bronchiole becomes blocked either by dust cells within or the pressure of fibrous tissue without; the air in the alveoli is absorbed and they collapse; the fibrous tissue forming in the alveolar walls coalesces with the fibrous tissue in neighboring collapsed walls and the alveolus can no longer be opened up. Though some of this dust will remain throughout the further development of the nodule, some will continue to escape till necrosis of the lymph channels which occurs late. White Haven Sanatorium Case No. 7518. Roentgenological and pathological third stage anthracosilicosis with tuberculosis, though none of the latter appears in this picture. Magnification 77

FIG. 3. Recently formed fibroanthracosilicotic nodule in act of approximating and coalescing with old one. The latter shows hyalinization of the marginal and necrosis of the interior collapsed alveolar walls. The lymphatics on the interior are also necrosed thus preventing further escape of dust from this time forward. The recently formed nodule is a lower magnification of that seen in fig. 2. Emphysema of the surrounding alveoli with fibrous tissue growth in their walls is also well shown. The old nodule is only on first glance single, being really formed by coalescence of several as is indicated by different vessels around which they developed. Same case as fig. 2. Magnification 27

FIG. 4. Spherical anthracosilicotic nodule 2 mm. in diameter appearing macroscopically to be a jet black single nodule is shown microscopically to be made up of more than one hundred smaller coalesced nodules. Each small area around a vessel represents an original microscopical nodule similar to those seen in fig. 3, except in a more advanced stage. Some nodules fail to show a central vessel because it has necrosed and others because of the plane of section. In the coalescence of nodules the fibrous tissue surrounding them is sometimes pulled into whorls which are accidental and not essential to the condition. White Haven Sanatorium Case No. 7909. Roentgenological and pathological third-stage anthracosilicosis without tuberculosis. Magnification 31

FIG. 5. Upper part of lung showing genuine emphysema with dilatation of alveoli due to loss of elastica. It also shows minute anthracosilicotic nodules made up only, or principally, of the thickened fibrous tissue associated with lymph channels around blood vessels, and other larger ones to which are evidently added collapsed alveoli. White Haven Sanatorium Case No. 7909. Roentgenological and pathological third stage anthracosilicosis without tuberculosis. Magnification 31

FIG. 6. Anthracosilicosis of lymph node showing increase of interstitial fibrous tissue due to the irritation of the dust and gradual elimination of follicles by pressure. White Haven Sanatorium Case No. 7556. Magnification 23

Shortly after, terminal bronchioles of affected lobules become blocked either by the accumulation of dust within or the pressure of newly formed fibrous tissue without, thus preventing ingress of air. The air present in the alveoli is absorbed and they collapse. Due to the continued presence of the silica dust, fibrous tissue continues to develop and the collapsed alveolar walls coalesce. From this time forward these alveoli can no longer be opened up (figure 2).

The next visible advance is hyaline degeneration of the newly formed fibrous tissue (figures 3 and 4). Since this occurs only on failure of the blood supply and since the arterioles and venules are visible until late in the disease, it must have been preceded by destruction of capillaries in this fibrous tissue. On still further advance this hyalinized fibrous tissue and the cells containing the dust undergo necrosis which begins in the interior of the nodule and leaves this interior composed of a mass of mineral dust.

This is also a result of the failure of the blood supply which is most marked on the interior of the nodule and less so outwards for the reason that the interior derives its blood supply entirely from the capillaries within the nodule which are destroyed early while the exterior derives some from functioning capillaries in the more or less normal tissue surrounding the nodule. As a consequence the dust cells and the lymphatics on the interior necrose first thus preventing removal of the dust granules which run together in a mass; while the lymphatics on the exterior continue to function till most of the dust is carried away, though by this time this exterior is also showing degeneration in the way of hyalinization. A nodule is thus presented with hyaline degenerated fibrous tissue with very little dust on the exterior and a mass of dust in the midst of necrosed cellular and fibrous tissue on the interior (figure 3). With no organic matter to act as a cushion between the granules of this interior dust, the knife grates as it cuts through.

This fibroanthracosilicotic nodule almost always contains a blood vessel situated sometimes centrally, sometimes excentrically. This blood vessel might easily lead to the idea that anthracosilicosis is a perivascular condition, that is, has some pathological relationship to the blood vessel, but this is not true. Anthracosilicosis acts principally on alveoli and ultimate bronchioles, destroying their walls and their contained capillaries, and replaces the walls by fibrous tissue. The participation of larger blood vessels in the disease is a late manifestation when we find

endarteritic and endophlebitic changes and eventual destruction due to pressure of the surrounding accumulation of mineral dust.

To understand the presence of the blood vessel within the anthracosilicotic nodule it is only necessary to recall the anatomy of the pulmonary lobule. In the centre of the lobule is the arteriole and bronchiole surrounded by alveoli. Running down outside the lobule is the venule. In anthracosilicosis the walls of the alveoli lose their elastica, become fibrous and collapse and since these alveoli surround an arteriole and bronchiole we should see a nodule with an arteriole and bronchiole within. The walls of the bronchiole, however, are affected in the same way as the alveoli, that is, they become fibrous and collapse with them in such a fashion that the alveoli and bronchioles are indistinguishable. This makes the nodule appear as a mass of collapsed alveoli about an arteriole alone.

Further the alveoli collapse around the arteriole not on account of a pathological relationship, but only because anatomically they surround it. This is proved by the fact that the vessel seen in the nodule is frequently a venule, though the venule runs in the interstitial tissue between lobules and is thus entirely separated from the alveoli. This interstitial tissue, however, is so small in amount as to be almost invisible and the alveoli seem to surround the venule similarly to the arteriole though the collapsed alveoli on two sides of the venule will be in two separate lobules.

The fact that the venule is found within the silicotic nodule so frequently shows that the collapse of alveoli even in an individual lobule is not uniform, that some collapse so as to give the impression of collapse about the arteriole in the middle, while others near the margin collapse so as to give the impression of collapse about the venule though the venule is outside the lobule. As the alveoli at the margin collapse without pathological relationship to the venule which is definitely separated from them, it is to be assumed the alveoli at the centre collapse without pathological relationship to the arteriole. In other words, the collapse of alveoli and the development of the anthracosilicotic nodule bear no relation to the blood vessels except an accidental anatomical one.

Returning now to the thickening of the interstitial tissue framework of the lung due to the irritation of the dust in its lymph channels, we find that though this adds to the fibrous tissue in the developing nodules it changes but little the picture already presented. This added fibrous

tissue is represented by strands around or alongside the blood vessel within the nodule (figures 2, 3 and 5), and by strands around the nodule, both showing cells filled with dust in lymphatics. Most of the dust in the fibrous tissue around the vessel on the interior of the nodule is retained on account of early necrosis of the fibrous tissue and its contained lymphatics; while a considerable amount of the dust in the fibrous tissue around the exterior of the nodule is squeezed out or carried away through lymphatics before they have been destroyed.

Eventually, then, the typical fibroanthracosilicotic nodule consists of a blood vessel surrounded by dust in necrotic lymphatics surrounded in turn by dust in collapsed alveoli and in their necrosing and necrotic walls, and further surrounded in turn by dust in lymphatics of newly formed fibrous tissue in connection with the fibrous tissue framework of the lobules.

Sometimes the collapse of alveoli in two lobules is around an accumulation of dust in an intrapulmonary lymph node situated in the crotch of a blood vessel or bronchiole, though much more commonly the former. This merely means that in the nodule thus formed there is somewhat more dust in the centre associated with the framework lymphatics than in the majority of nodules without changing materially the picture.

This description of the primary anthracosilicotic nodule practically completes the description also of the larger nodules, which are merely a number of smaller ones run together. For instance, in figure 4 (a case of pure anthracosilicosis without tuberculosis) we have what appeared macroscopically to be a single dense black fibroanthracosilicotic nodule 2 mm. in diameter. Microscopically we find this spherical nodule, in spite of its small size, to be a conglomerate nodule consisting of more than one hundred separate nodules with a blood vessel in the majority of them. These nodules have in places coalesced and in others are in such close proximity to one another that no macroscopical separation is visible. Larger nodules, even up to four or more centimetres in diameter, show a similar microscopical appearance except, instead of being made up of a hundred, they are made up of many many thousand separate nodules.

Coalescing nodules are often of different ages and sometimes old ones with markedly contracted fibrous tissue coalesce with others recently formed or in the act of forming and pull them so out of shape and sometimes into peculiar whorls as to give the impression that they developed

in a different way (figure 4). With the preceding description in mind, it requires but little study to separate the different nodules making up a large nodule and recognize what has happened.

Sometimes on the interior of a large nodule we find a ragged cavity showing serrated walls, devoid of a pyogenic membrane, from which has been expelled some of the dust and of the debris of necrosed cells and tissue composing the centre of the nodule. Sometimes even corrosion of a blood vessel before its complete elimination is accompanied by more or less severe haemoptysis. On account of the walls and contents of these cavities being deep black, the condition has sometimes been called *phthisis atra.*

Whether or not these cavities can occur in pure anthracosilicosis uncontaminated by tuberculosis has not been settled, though it is quite sure from animal inoculation that many fail to contain tubercle bacilli. Since these cavities are not very common and are only rarely multiple, it has been suggested that they represent the clearing out of an old primary affect with further extension of the necrotic wall. This is a possible explanation even for the multiple cavities, since rarely the primary affect in the lung is multiple.

In addition, both apart from and in connection with the nodules, anthracosilicotic dust in small amounts is sometimes found in epithelial cells lining alveoli and bronchioles, in cartilage cells of bronchial walls, in intimal cells of blood vessels, in cancer cells when this tumor is an associated pulmonary complication, and in leucocytes in the blood-stream. These, however, are merely interesting findings practically limited to advanced cases, which show how widely distributed the dust can be without specifically influencing the ordinary development of the anthracosilicotic nodule.

At necropsy then we see anthracosilicosis in four stages or forms (1): (*1*) the predominant lymphatic form in which we find macroscopically black lines extending toward the hilum nodes which in cross section are visible as minute black specks; (*2*) the nodular form in which we find in addition to the black lines a stippling of the lung with shot-like or larger nodules; (*3*) the diffuse indurative form in which we find masses of fibrosis and dust making up the typical huge fibroanthracosilicotic nodule composed of an immense number of smaller nodules run together; (*4*) the ulcerative or cavernous form with ragged cavities on the interior of large nodules.

THE SILICOTIC LYMPH NODE NODULE

In spite of the fibroanthracosilicotic nodule in the hilum lymph node appearing macroscopically similar to that in the lung there are certain differences. The pulmonary nodule is made up principally of successive layers of fibrous tissue in the walls of collapsed alveoli and to a lesser extent of fibrous tissue around lymphatics in the framework of the lobules. The lymph node nodule consists entirely of fibrous tissue around lymphatics in the framework of the node.

A normal lymph node is made up principally of follicles in which lymphocytes are manufactured; each follicle is surrounded by a lymph sinus which has no direct communication with it and this sinus is in turn surrounded by the fibrous tissue framework. The afferent lymph vessel enters the node at the periphery and proceeds through the framework to the lymph sinus. The dust cells carried to the node accumulate in the lymph sinus and the framework, and the irritation of their presence causes the formation of the new fibrous tissue in these situations. Hence in early stages the black fibroanthracosilicotic nodule remains practically the shape of the original node and still shows lymph follicles as whitish specks (figure 6). As the disease advances the follicles are compressed out of existence by the developing fibrous tissue and the nodule enlarging assumes a shape determined by the pressure of surrounding tissue.

On account of the failure of direct communication between the afferent lymphatics and the follicles, the latter should exhibit no dust. Yet sometimes a follicle develops embryologically around a blood vessel and the lymphatics in the vessel wall may show dust which thus appears to be within the follicle, but both anatomically and physiologically the two will be separated. Rarely, too, in far advanced cases a small amount of dust may be found in a follicle which has accidentally escaped destruction just as granules of dust may be found in epithelial cells of pulmonary alveoli, but these findings are apart from the regular and usual development of the condition.

SUMMARY

Anthracosilicotic dust within the tissues of the lung is always found in cells until after necrosis sets in. These cells are carried in lymph channels to intrapulmonary and hilar nodes. The pulmonary fibroanthracosilicotic nodule begins by thickening of the interstitial tissue around lymphatics, the development of fibrous tissue in alveolar walls

and destruction of the elastica which allows the alveoli to collapse. The typical single nodule is smaller than a millet seed and is made up principally of collapsed and coalesced alveolar walls. Later occur hyalinization and necrosis beginning in the interior. A large nodule is always conglomerate, and is made up of the coalescence of innumerable small ones. The silicotic nodule in lymph nodes is also described and how it differs from the pulmonary nodule.

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SEDIMENTATION RATE OF RED BLOOD CELLS IN PLASMA, PLEURAL AND ASCITIC FLUIDS[1]

SAMUEL COHEN, PHILIP FARACI AND BERTHOLD S. POLLAK

While knowledge of the phenomenon of sedimentation of erythrocytes can be traced back to ancient times, it is only in comparatively recent years that it has become the subject of considerable study during which time a rather extensive literature has accumulated. Variations in the rapidity of sedimentation have been attributed (excluding technical factors) to: (*1*) alteration of the electrical charge of particles suspended in the blood; (*2*) alterations in viscosity and surface tension; (*3*) changes in the red blood cells affecting the number, size and haemoglobin content; (*4*) quantitative fluctuations in some constituents of the plasma, particularly of fibrinogen, globulin and albumin.

The sedimentation rate has come to be looked upon as an indicator of the degree of tissue breakdown going on in the body. However, it is not a specific test and is influenced by many different destructive processes. One of its chief reputed clinical uses is as an aid in evaluating activity or quiescence of some infectious diseases.

A natural inference from the above mentioned elements that influence sedimentation speed is that suspensions of red blood cells in different organic fluids may vary in the speed of sedimentation. By suspending red blood cells in plasma and other tissue fluids, namely, pleural and ascitic effusions, we have tried to determine: (*1*) whether an index to the degree of inflammation of the aspirated serous cavity can be obtained; (*2*) whether an adequate differential test between a transudate, a serofibrinous exudate and a purulent exudate is possible.

The material has been drawn largely from the Tuberculosis Service. Pleural tuberculous exudates with or without associated artificial pneumothorax lend themselves readily to this study. Several other types of effusions were derived from patients on the general medical service of the hospital. Somewhat similar studies, but on a less extensive scale, were reported by Popper and Kreindler (1925) (1), Garnier and Oumansky (1926) (2), Radossavlievitsch (1927) (3). Kling (1932) (4) carried

[1] From the Tuberculosis Service, Medical Center, Jersey City, New Jersey.

out the same plan with synovial fluids. We have adopted the latter's technique for our work.

METHODS OF STUDY

Twelve cc. of venous blood were added to a test tube containing 3.0 cc. of 3.8 per cent sodium citrate solution; 6.0 cc. were then transferred to a centrifuge tube and centrifuged at high speed for ten minutes simultaneously with another tube containing 2.0 cc. of 3.8 per cent sodium citrate solution plus 8.0 cc. of pleural or ascitic fluid. The tube with citrated blood was then marked at the lower and upper levels of the separated plasma. The latter was then carefully pipetted off and replaced by an equal amount of the supernatant pleural or ascitic fluid. A suspension of red blood cells in the fluid equivalent to that in the citrated blood was thus obtained. This suspension and the remainder of the original citrated blood were shaken separately and each was drawn into a pipette (lumen = 4.0 mm. in diameter), marked at a height of 20 cm. The tubes were set up vertically in a rubber stopper. The separation of erythrocytes from the fluid was marked off every hour for the first 8 hours. Final readings were made in 24 hours. It has been shown that interruption of sedimentation and subsequent resuspension produce no significant change in the readings, and that the sedimentation rate is affected little if the cells are washed in saline prior to their addition to the effusion.

The following supplementary determinations were made on specimens of the original noncitrated fluid as soon after aspiration as possible: (*1*) color and consistency; (*2*) specific gravity, measured with an urinometer; (*3*) quantitative estimation of protein (Purdy centrifugal method, results expressed in grams of dry protein per 100 cc. of fluid); (*4*) differential cell count; (*5*) smear for microörganisms; (*6*) culture or guinea-pig injection in selected cases.

To determine the average sedimentation rate of normal blood according to the method outlined above, 50 apparently normal individuals were selected.

DEFINITION OF TERMS

The traditional definitions of a transudate and an exudate are as follows: The former is a noninflammatory effusion caused by general or local circulatory disturbances, while the latter is an inflammatory effusion produced by various irritants, chemical, physical or bacterial. The

common tests employed for their differentiation need not be repeated here, but suffice it to say that at times the problem is not easily solved. It is important to remember also that, under some conditions, the fluid may be an admixture of the two.

In describing sedimentation curves, the accepted terminology of straight line, diagonal line, vertical line and vertical curve will be applied.

The comparative sedimentation index (Kling) is the ratio, at the end of any given time interval (usually one hour), between the sedimentation reading of the red blood cells in the pleural or ascitic fluid and the reading of the sedimentation in the plasma, that is, $\frac{\text{S.F.}}{\text{S.P.}} = \text{C.I.}$

SUMMARY OF MATERIAL

Total number of cases: 61
Total number of sedimentation rate readings: 153

Type of fluid	*Number of cases*	*Number of sedimentation rate readings*
I. *Pleural transudates*		
Secondary to cardiac decompensation	9	16
II. *Peritoneal transudates*		
Secondary to cirrhosis of the liver	5	8
Secondary to amyloidosis of the liver	1	
III. *Pleural exudates*		
Tuberculous		
Serous		
Associated with artificial pneumothorax		
Spontaneous effusions	17	42
Effusions secondary to artificial mediastinal fixation	4	11
Not associated with artificial pneumothorax	13	18
Purulent		
Associated with artificial pneumothorax	6	18
Transition from serous to purulent exudate		
Associated with artificial pneumothorax	5	31
Effusion secondary to lobectomy	1	9

RESULTS

The sedimentation rate of red blood cells of fifty apparently normal individuals according to the method outlined above gave the following results: The lowest and highest 1-hour sedimentation rates were 1.0 mm. and 16 mm. respectively with an average of 6.0 mm. The two extremes of the 24-hour drop were 29 mm. and 147 mm., and 80 mm. was the average.

Pleural Transudates

Total number of cases	9
Total number of sedimentation rate readings	16
Average specific gravity	1.012
Average quantitative protein	0.6566 gm.
Average sedimentation rate in pleural transudates—1 hr.	5.0 mm.
Average sedimentation rate in pleural transudates—4 hr.	22.0 mm.
Average sedimentation rate in pleural transudates—24 hr.	46.0 mm.
Average sedimentation rate in plasma—1 hr.	29.0 mm.
Average sedimentation rate in plasma—4 hr.	68.0 mm.
Average sedimentation rate in plasma—24 hr.	100.0 mm.
Average comparative sedimentation index—1 hr.	17.2%
Average comparative sedimentation index—4 hr.	32.3 %
Average comparative sedimentation index—24 hr.	46.0 %

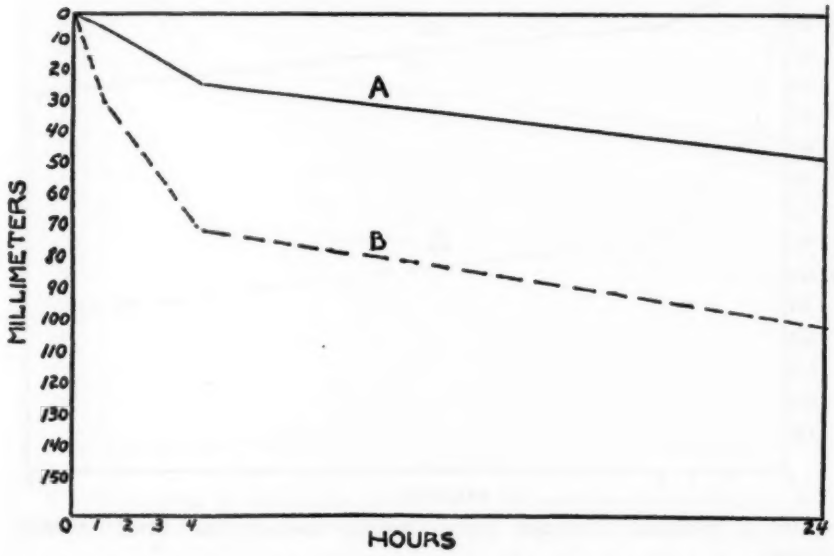

CHART 1. Pleural transudate group. Average sedimentation curves. A—fluid. B—plasma.

In all these cases, the hydrothorax was secondary to myocardial insufficiency. The fluids were yellow in color and showed few lymphocytes. The specific gravity ranged from 1.008 to 1.016. Only one fluid contained as much as 1.040 gm. of protein; the lowest protein content was 0.3328 gm.

The important observations were: (*1*) that, in 13 out of the 16 sedimentation rate findings, the fluid curve was a horizontal line; the remaining three showed diagonal lines; (*2*) that the sedimentation of the erythro-

cytes in the transudates was in all cases less than that in the patient's own blood plasma. The low protein content of these effusions undoubtedly accounted for the course of sedimentation.

Peritoneal Transudates

Total number of cases	6
Total number of sedimentation rate readings	8
Average specific gravity	1.011
Average quantitative protein	0.8195 gm.
Average sedimentation rate in peritoneal transudates—1 hr.	3.0 mm.
Average sedimentation rate in peritoneal transudates—4 hr.	16.0 mm.
Average sedimentation rate in peritoneal transudates—24 hr.	40.0 mm.

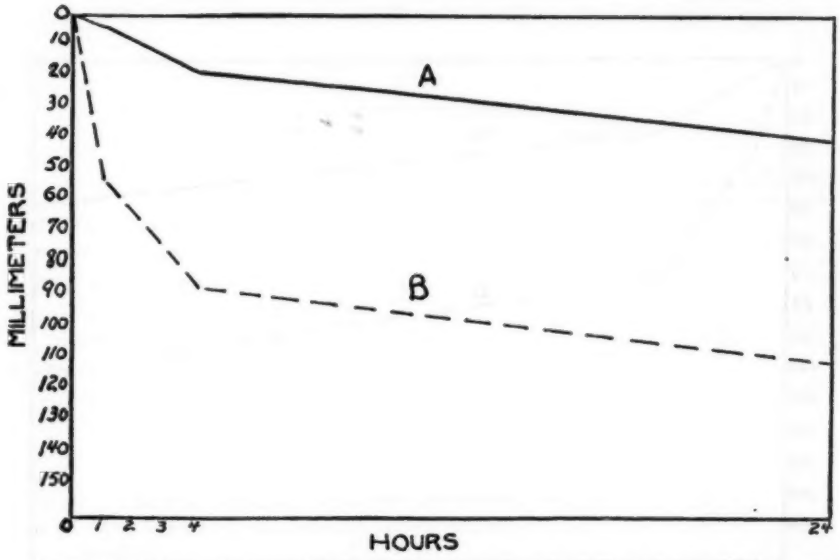

CHART 2. Peritoneal transudate group. Average sedimentation curves. A—fluid. B—plasma.

Average sedimentation rate in plasma—1 hr.	53.0 mm.
Average sedimentation rate in plasma—4 hr.	87.0 mm.
Average sedimentation rate in plasma—24 hr.	111.0 mm.
Average comparative sedimentation index—1 hr.	5.6 %
Average comparative sedimentation index—4 hr.	20.7 %
Average comparative sedimentation index—24 hr.	36.0 %

Five of these 6 cases showed clinical evidence of cirrhosis of the liver. Two of these also had pulmonary tuberculosis and postmortem examination later revealed, in addition, subcapsular tubercles and some within the parenchyma of the liver. One of the patients, with a superimposed acute generalized haematogenous tuberculosis, exhibited many tubercles

in the main serous membranes, including the peritoneum. It is probable that the ascitic fluid in this instance was a combination of a transudate and an exudate. The only sedimentation reading of the fluid in this case indicated a transudate. The sixth patient had a far advanced bilateral pulmonary lesion with a markedly enlarged liver due to amyloidosis which was confirmed by necropsy. The fluid was thin, opalescent, pseudochylous and interestingly enough showed the lowest specific gravity (1.007) and the lowest protein (0.208 gm.) of any of the transudates examined.

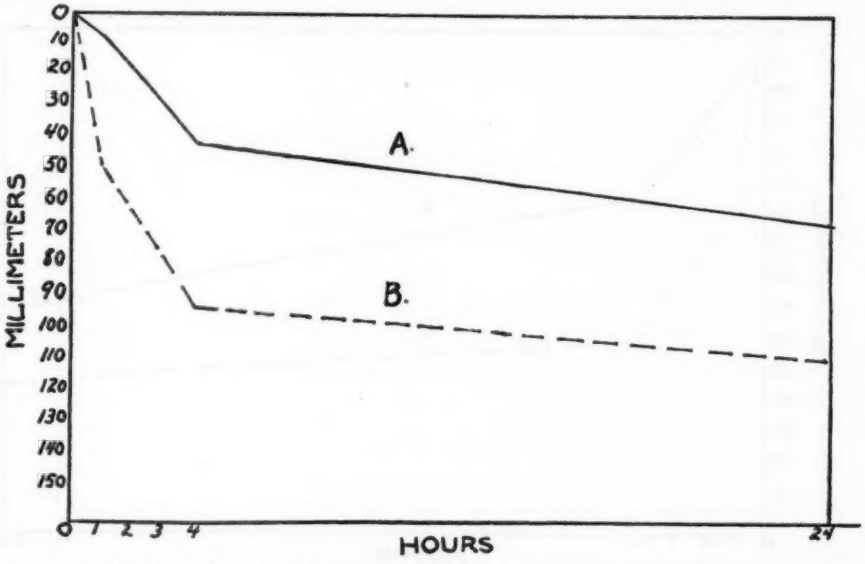

CHART 3. Group of tuberculous serous fluids with artificial pneumothorax. Average sedimentation curves. A—fluid. B—plasma.

Practically all the results in this group closely paralleled those of the thoracic transudates. The highest specific gravity was 1.017. The peak of the protein was 1.1480 gm. The average total drop was lower than that in the plasma. Six curves were horizontal lines and two were diagonal lines.

Tuberculous Serous Effusions Complicating Artificial Pneumothorax

Total number of cases	17
Total number of sedimentation rate readings	42
Average specific gravity	1.018
Average quantitative protein	1.1406 gm.
Average sedimentation rate in serous effusions—1 hr	7.0 mm.

Average sedimentation rate in serous effusions—4 hr	41.0 mm.
Average sedimentation rate in serous effusions—24 hr	66.0 mm.
Average sedimentation rate in plasma—1 hr	48.0 mm.
Average sedimentation rate in plasma—4 hr	93.0 mm.
Average sedimentation rate in plasma—24 hr	109.0 mm.
Average comparative sedimentation index—1 hr	14.6 %
Average comparative sedimentation index—4 hr	43.0 %
Average comparative sedimentation index—24 hr	60.5 %

This group comprised the largest number of cases (17) with the greatest number of serial sedimentation rate studies (42). All patients had moderately or far advanced tuberculosis. The effusions occurred during

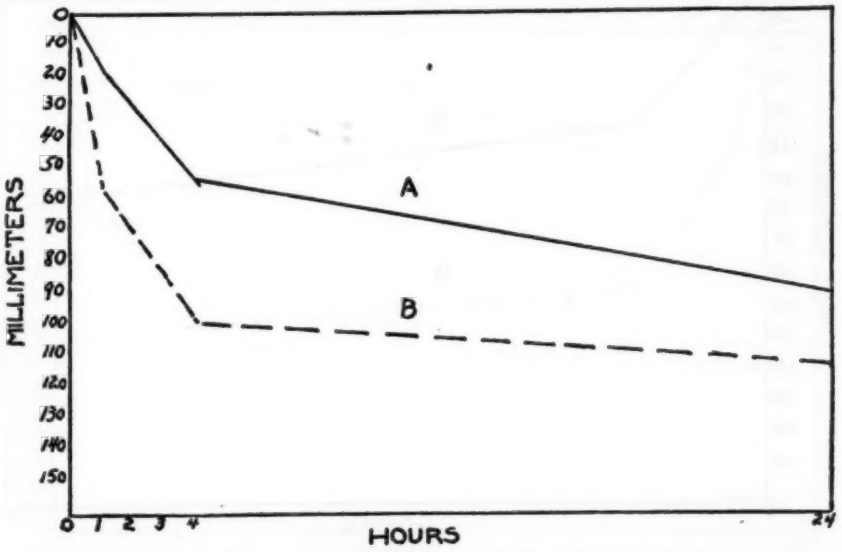

CHART 4. Group of tuberculous serous fluids without artificial pneumothorax. Average sedimentation curves. A—fluid. B—plasma.

the active phase of pneumothorax therapy and not at the time of re-expansion, so that *a priori* they should be considered as exudates. Cytological study revealed a predominance of lymphocytes in most of these fluids, although several in the acute phase of formation showed a considerable number of polymorphonuclear leucocytes. The lowest specific gravity was 1.012, this was noted in one determination of a case that had a total of 12 readings; and the maximum for the entire group was 1.024. The protein, as was to be expected, was also higher than that of the transudates; it ranged between 0.7280 and 1.3184.

The pertinent finding was a more rapid average sedimentation at the

end of 4 hours (41 mm.) than for the antecedent groups of transudates. With two exceptions, all the curves were of the diagonal type. In two cases, the fluid curves crossed the blood curves.

Tuberculous Serous Effusions Not Associated with Artificial Pneumothorax

Total number of cases	13
Total number of sedimentation rate readings	18
Average specific gravity	1.020
Average quantitative protein	1.1333 gm.

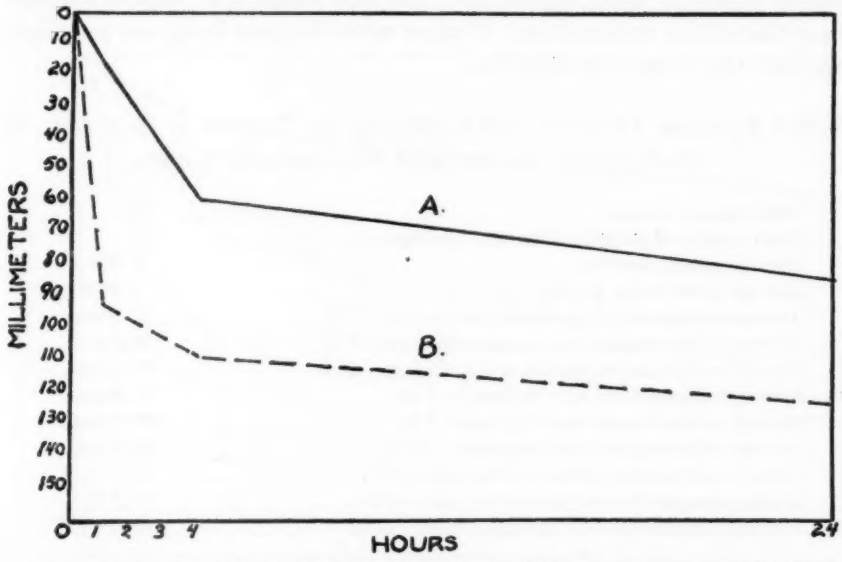

CHART 5. Group of chemically induced fluids in artificial pneumothorax cases for fixation of mediastinum. Average sedimentation curves. A—fluid. B—plasma.

Average sedimentation rate in serous effusions—1 hr	17.0 mm.
Average sedimentation rate in serous effusions—4 hr	53.0 mm.
Average sedimentation rate in serous effusions—24 hr	90.0 mm.
Average sedimentation rate in plasma—1 hr	55.0 mm.
Average sedimentation rate in plasma—4 hr	98.0 mm.
Average sedimentation rate in plasma—24 hr	113.0 mm.
Average comparative sedimentation index—1 hr	30.9 %
Average comparative sedimentation index—4 hr	54.0 %
Average comparative sedimentation index—24 hr	79.6 %

One case was that of a colored female child who had roentgen evidence of mediastinal adenopathy, thickened pleura (right) and subsequently developed a left-sided effusion. In two other cases, also undoubtedly

of haematogenous origin, fluid occurred in one pleural cavity and a few months later on the opposite side. One patient with far advanced pulmonary tuberculosis showed a pleural effusion. In the remaining nine patients, there were no X-ray signs of parenchymal disease but a diagnosis of tuberculous serofibrinous pleuritis was made in all on the basis of available clinical data and by the process of exclusion.

A similar cytological formula was apparent in this group as in the preceding serous exudates. The specific gravity ranged between 1.017 and 1.026. The protein fluctuated from 0.8744 to 1.2896 gm. All the curves showed a more rapid drop in the first 4 hours, 53 mm. in average, than that of the transudates. Sixteen were diagonal lines, one a straight line and the other a vertical line.

Serous Effusions Produced Artificially for the Purpose of Stiffening the Mediastinum in Artificial Pneumothorax Cases

Total number of cases	4
Total number of sedimentation rate readings	11
Average specific gravity	1.019
Average quantitative protein	1.2808 gm.
Average sedimentation rate in serous effusions—1 hr.	16.0 mm.
Average sedimentation rate in serous effusions—4 hr.	58.0 mm.
Average sedimentation rate in serous effusions—24 hr.	85.0 mm.
Average sedimentation rate in plasma—1 hr.	91.0 mm.
Average sedimentation rate in plasma—4 hr.	109.0 mm.
Average sedimentation rate in plasma—24 hr.	124.0 mm.
Average comparative sedimentation index—1 hr.	17.5 %
Average comparative sedimentation index—4 hr.	53.2 %
Average comparative sedimentation index—24 hr.	68.5 %

These cases of chemically induced exudates, although small in number, were very interesting and in a sense constituted a control group. The sterile irritants used were mineral oil, gomenol in mineral oil and 7 per cent saline.

The fluids were all thin and yellow in color with an early predominantly polymorphonuclear cell count. The specific gravity readings varied from 1.017 to 1.022. The protein content ranged between 1.0608 and 1.6640 gm. These estimations paralleled those obtained in serous exudates of bacterial origin. A comparison of the tabulations will show that the fluid sedimentation course in this group approached more closely that noted in the serous exudates unassociated with collapse therapy. Of interest also was the sharp, rapid drop of the blood curve at the end of the first hour with an average of 90 mm. For the entire

group of cases seven fluid curves were diagonal lines; two, vertical lines; one, vertical curve; one, horizontal line. It is instructive to report one of these cases in some detail.

T. H., a colored male, age 38, was admitted with far advanced tuberculosis 2/15/37. Right-sided pneumothorax was induced 3/18/37. On 5/17/37, 10 cc. of sterile mineral oil were injected into the pleural cavity. Fluoroscopy on the following day showed fluid to the eleventh posterior rib which increased one week later to the eighth rib. Fluid removed 6/1/37 had a specific gravity of 1.020 with 1.0608 gm. of protein. The sedimentation in the effusion was a vertical line with a sharp drop of 45 mm. in 1 hour, 90 mm. in 4 hours and 96

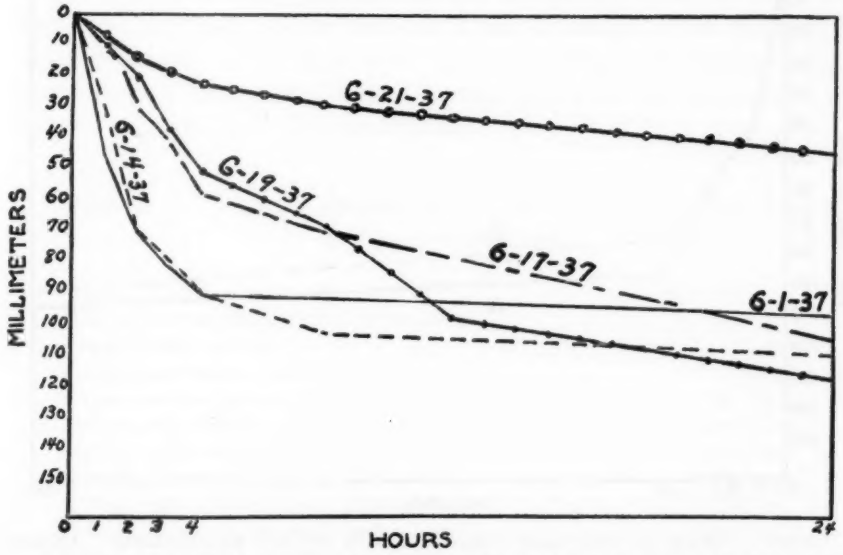

CHART 6. *T. H.* Fluid sedimentation curves. Ten cubic centimeters sterile mineral oil injected on May 17, 1937.

mm. in 24 hours. The blood showed a vertical curve with a drop of 112 mm. in 1 hour and 124 mm. in 24 hours. Reaccumulation and subsequent pocketing of the fluid occurred. The temperature slowly returned to normal limits. Four more comparative sedimentation determinations were made on June 14, 17, 19 and 21. While the blood curves showed slight variation, the fluid curves revealed a gradual change from a vertical to diagonal and finally to almost a straight line on 6/21/37 (chart 6). Thus, it is seen that the sedimentation rate of the erythrocytes in these fluids tended to run parallel *pari passu* with the degree of pleural inflammatory activity as judged by clinical and fluoroscopic standards.

Tuberculous Empyemata Secondary to Artificial Pneumothorax

Total number of cases	6
Total number of sedimentation rate readings	18
Average specific gravity	1.022
Average quantitative protein	1.3122 gm.
Average sedimentation rate in purulent effusions—1 hr	45.0 mm.
Average sedimentation rate in purulent effusions—4 hr	95.0 mm.
Average sedimentation rate in purulent effusions—24 hr	105.0 mm.
Average sedimentation rate in plasma—1 hr	47.0 mm.
Average sedimentation rate in plasma—4 hr	84.0 mm.
Average sedimentation rate in plasma—24 hr	100.0 mm.

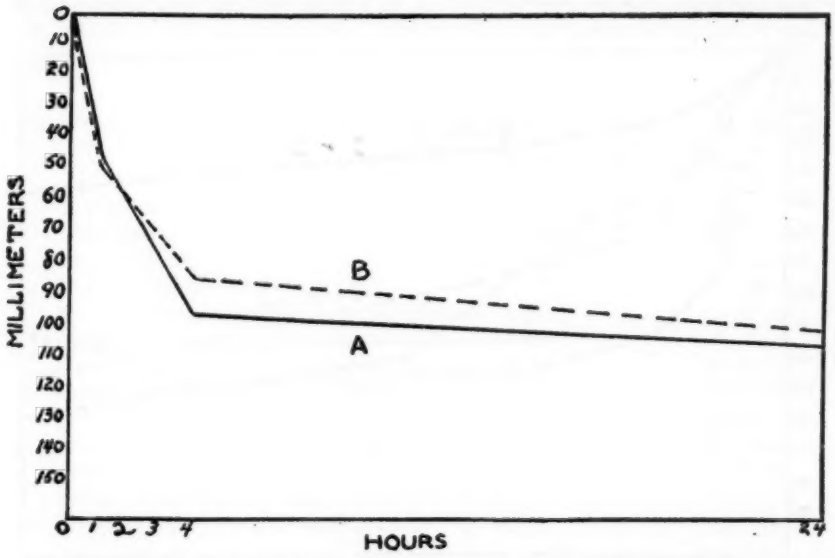

CHART 7. Group of tuberculous empyemata with artificial pneumothorax. Average sedimentation curves. A—fluid. B—plasma.

Average comparative sedimentation index—1 hr	91.4 %
Average comparative sedimentation index—4 hr	113.0 %
Average comparative sedimentation index—24 hr	105.0 %

The original parenchymal lesions in these 6 cases prior to collapse treatment were far advanced. At the time this study was begun, 5 of them already had a suppurating pleurisy due to tubercle bacilli. No pyogenic microörganisms were present at any time. These individuals attended the outpatient clinic and presented nontoxic empyemata. The last case was somewhat different. Artificial pneumothorax had been started on the left side in May, 1935 and discontinued for various reasons

in January, 1936. The patient returned to the hospital in September, 1937. The chest X-ray now showed a completely reëxpanded left lung with the exception of a very small residual encapsulated effusion which proved to be a seropurulent fluid containing tubercle bacilli. Very thick, stringy purulent exudates were found unsatisfactory for sedimentation tests.

The extremes of the specific gravity were 1.018 and 1.028. The protein ranged between 1.7888 and 0.9984 gm.

The outstanding finding was that, in 16 out of the 18 determinations, the sedimentation of the red blood cells in the effusions exceeded that in the patient's blood plasma so that comparative indices were very high, greater than 100 per cent for 4 and 24 hours. The fluid curves crossed the blood curves in five instances. The characteristic graphs were vertical lines and vertical curves indicating an increased local pleural reaction with much exudation.

Effusions in Artificial Pneumothorax with Transition from Serous to Purulent Exudates

Total number of cases	5
Total number of sedimentation rate readings	31
Average specific gravity	1.0245
Average quantitative protein	1.2863 gm.
Average sedimentation rate in pleural effusions—1 hr.	55.0 mm.
Average sedimentation rate in pleural effusions—4 hr.	104.0 mm.
Average sedimentation rate in pleural effusions—24 hr.	116.0 mm.
Average sedimentation rate in plasma—1 hr.	93.0 mm.
Average sedimentation rate in plasma—4 hr.	112.0 mm.
Average sedimentation rate in plasma—24 hr.	119.0 mm.
Average comparative sedimentation index—1 hr.	59.1 %
Average comparative sedimentation index—4 hr.	92.8 %
Average comparative sedimentation index—24 hr.	97.4 %

This group of cases which was followed during the period of transition from serous to purulent tuberculous effusions was considered a fertile one in which serial determinations would be useful to test the significance of the general tendencies exhibited by the sedimentation rates in the preceding groups of exudates. The sedimentation characteristics previously alluded to were substantiated.

The transition from one type of fluid to another constituted a sign of active tuberculous pleuritis. This, we believe, was adequately reflected by the relatively high sedimentation figures that were obtained

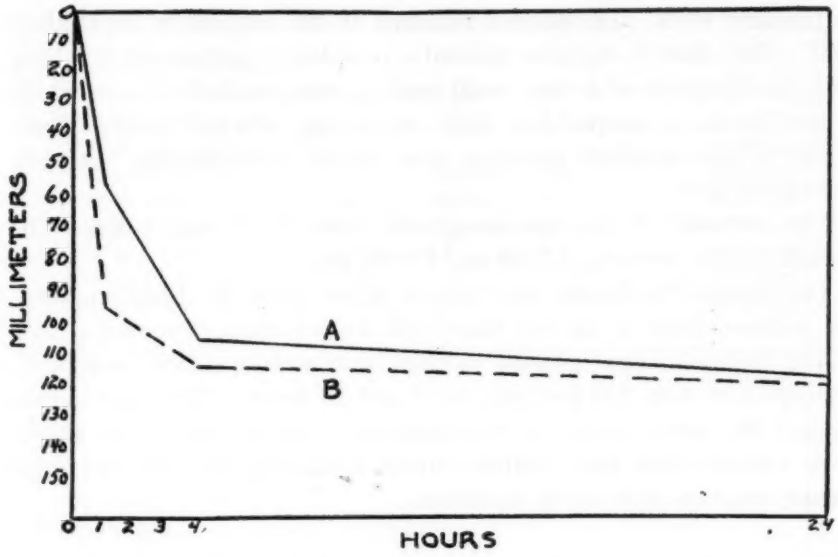

CHART 8. Group of transition fluids from serous to purulent in artificial pneumothorax cases. Average sedimentation curves. A—fluid. B—plasma.

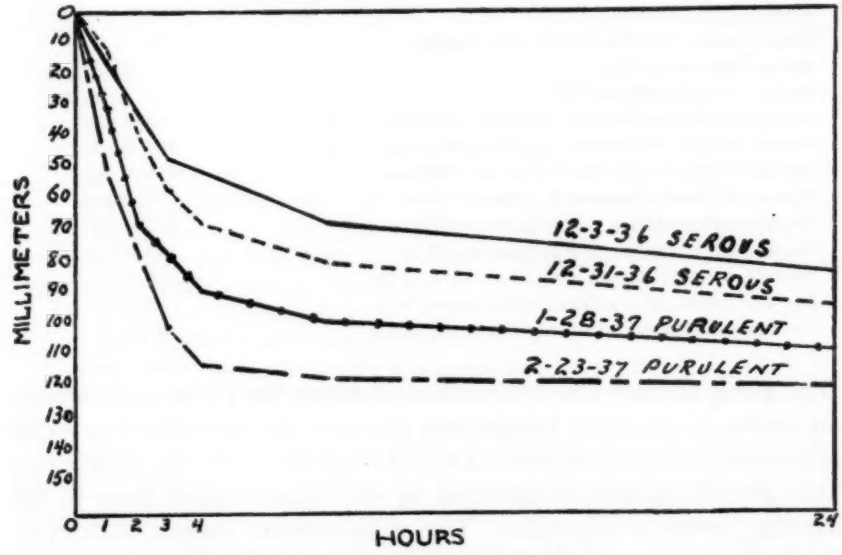

CHART 9. *C. G.* Fluid sedimentation curves

in the effusions and by a comparison of the serial curves. Chart 9 shows four fluid curves in a patient belonging to this group.

Effusion Secondary to Lobectomy

H. G., a twenty-five year old nurse, had a single-stage lobectomy for a tumor mass in the left lower lobe on April 7, 1937. Her postoperative course was very good and she was discharged on May 27, 1937.

As a preliminary procedure to operation, left-sided artificial pneumothorax had been induced on March 24, 1937. No fluid formed preoperatively. A postoperative film (April 12) showed an almost complete collapse of the remaining lung on the left with a small amount of fluid in the sulcus; this increased in amount. Straw colored, slightly serosanguinous fluid was aspirated on nine occasions in the interval between April 19 and May 20, 1937. Smears and cultures were sterile. The specific gravity ranged between 1.015 and 1.018 and the protein from 1.040 to 1.240 gm. The average sedimentation rates in the effusion in 1, 4 and 24 hours were 4 mm., 23 mm. and 52 mm., respectively. The corresponding figures for the blood curve were 85 mm., 117 mm. and 123 mm. with comparative indices of 4.7 per cent, 19.6 per cent and 45.5 per cent.

Five fluid sedimentation curves were diagonal lines and four horizontal lines. It was logical to assume that the pleural effusion, particularly at the very outset, was an exudate as a response to surgical manipulation and that this fluid soon became diluted by a transudate due to the high negative intrapleural pressure attendant on resection of a lobe. The laboratory data and comparative sedimentation studies confirmed this impression.

COMMENT

In all fairness, mention must be made of certain factors which help determine the composition of effusions and also probably influence the fluid sedimentation rate. These factors are not always easy to evaluate and no thorough correlative studies were made in our work to show their relationship to the particular problems at hand: (*1*) the duration of the effusion—in chronic cases it is assumed that absorption of water will produce a relative increase in the protein constituents (Wells) (5); (*2*) the composition of the patient's blood—cachectic persons will show a lower proportion of protein in effusions than well nourished ones (Wells) (5); (*3*) the status of the specifically involved serous cavity—particularly as regards capillary permeability (Pinner and Moerke) (6). A virgin and a thickened serosa will reveal variations in this respect and thus will alter the chemistry of effusions. Also, other things being equal, capillary permeability varies with the different serous membranes in any given individual, depending on local or intrinsic conditions.

It is important to remember that, especially in the cases of tuberculous

exudates concomitant with collapse therapy, the blood sedimentation rates represented a more or less useful index of the systemic reaction, embracing pleuropulmonary disease, or extrapulmonary lesions, or both. With the fluid sedimentation studies, however, an attempt was made to visualize the rôle played by the single component of tuberculous pleurisy as part of the entire clinical picture.

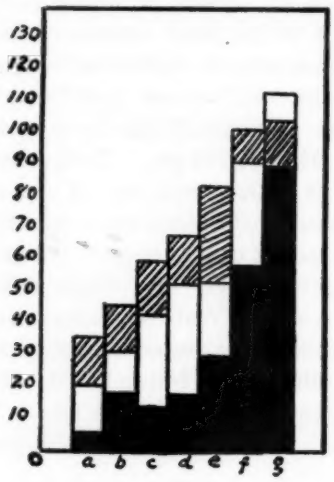

CHART 10. Average comparative sedimentation indices. a—peritoneal transudates; b—pleural transudates; c—serous fluids with artificial pneumothorax; d—serous fluids for fixation; e—serous fluids without artificial pneumothorax; f—transition from serous to purulent fluids; g—tuberculous empyemata. ■—1 hr. comparative index. □—4 hr. comparative index. ▨—24 hr. comparative index.

SUMMARY AND CONCLUSIONS

1. The technique of Kling was employed in obtaining comparative sedimentation curves of pleural and ascitic effusions and of the patient's own plasma. The material comprised a total of 61 cases in which 153 fluid sedimentation rate determinations were made and an equal number of blood readings. Pertinent additional laboratory tests were made on the aspirated fluids. The blood sedimentation rates (according to the modified Westergren method) on fifty apparently normal individuals were also determined.

2. The results of comparative sedimentation taken in groups were quite constant. This cannot be emphasized too strongly, for individual cases will show variations from the average findings. The latter do *not*

represent absolute lines of cleavage which are always applicable in every instance. With these preliminary remarks, we note:

(a) The sedimentation of erythrocytes, in general, is rapid in inflammatory effusions having a high protein content, and low in fluids of noninflammatory origin having a low protein content. This confirms the conclusion of Garnier and Oumansky. Coincidently, the former show a high comparative index which reaches its maximum with purulent tuberculous exudates and the latter a low index. "The comparative index reveals the share that the local process contributes to the general reaction." (Kling.)

(b) The fluid sedimentation rates at the end of one and four hours were found to be most significant. In transudates (pleural and ascitic) the average sedimentation is less for these time intervals than the average rate in normal plasma and in the patient's plasma. In exudates, as a rule, sedimentation exceeds that in normal plasma. This observation may be added to the list of tests utilized for the differentiation between these two types of effusions. Our work was limited to tuberculous and sterile chemical exudates but there is reason to assume that exudates as as class conform to this pattern.

(c) Using the patient's cells, the typical fluid sedimentation curves for the effusions studied were: (*1*) transudate: a horizontal line; (*2*) serous exudate: a diagonal line; (*3*) purulent exudate: a vertical line or curve. (See charts.)

(d) Again, considered as unit groups, there is noted some parallelism between the average specific gravity, the average quantitative protein and the average type of fluid curve.

(e) Comparison of serial fluid curves may be employed as a laboratory adjunct to determine regression or progression of exudation in tuberculous pleuritis. Clinical and radioscopic examinations still remain of paramount importance, however.

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PRONTOSIL IN EXPERIMENTAL TUBERCULOSIS[1]

A Preliminary Report

HARRY F. DIETRICH[2]

There is a valid experimental and clinical proof of the value of sulphanilamide and related dyes in a great variety of pyogenic infections (1); the question of their possible use in chronic granulomatous infections has so far received no attention. Sooner or later some curious or enthusiastic user of the drugs will try their effect on tuberculous patients. Before doing so it would be well to consider the pertinent fact that the pathology of granulomatous and acute pyogenic infections is not analogous. In meningococcus meningitis, streptococcus septicaemia, colon bacillus pyelitis, and even erysipelas, the offending microörganisms can be reached readily by blood- and lymph-borne drugs. In tuberculosis the microörganisms are isolated in relatively avascular lesions. Fibroblasts and epithelioid cells wall off the area, and the central portion ultimately proceeds to an avascular necrosis (caseation) which provides an almost impregnable barrier to intercellular fluids. It becomes evident that even if a drug killed tubercle bacilli *in vitro* there would be no theoretical basis for hoping for a similarly favorable result *in vivo*. Because of the foregoing considerations, and because prontosil is not effective until it is reduced in the body, no *in vitro* studies were attempted.

CHOICE OF DRUG

The di-sodium salt of 4-sulphamido-phenyl-2-azo-7 acetylamino-l-hydroxynaphthalene-3,6-disulphonic acid in a 2.5 per cent solution (previously and hereafter referred to by one of its trade names, "prontosil") was selected. Although some of the more recent work has shown that this complex dye has greater toxicity than has sulphanilamide (2), the former drug has been used in various acute infections with good results (3). Much of the early work on streptococcus peritonitis in mice was done with prontosil (4), and there is no doubt of its bactericidal

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action when it is reduced in the animal body. Prontosil was chosen for the present studies because it was readily available and it lent itself to intraperitoneal administration; sulphanilamide should receive a similar trial.

PROCEDURE

Animals A, B, 1, 2, 3 and 4 were given 0.5 cc. of a suspension of tubercle bacilli recovered from the lung of a patient dying of tuberculosis; the remaining animals were injected with 0.25 cc. of the suspension. All inoculations were made subcutaneously just cephalad to the right groin. This site was chosen because of the ease of following the involvement of the inguinal glands.

The prontosil administered was injected into the peritoneal cavity in single daily doses of 100 mg. per kilogram of body weight. This dosage is considerably in excess of amounts that have proved effective in curing acute pyogenic infections in mice and guinea pigs.

Complete autopsies were done on each animal. Where there was any doubt about the interpretation of gross findings, sections were taken for microscopical study. No animal showed any peritoneal reaction to the injected prontosil.

OBSERVATIONS

When guinea pigs are inoculated subcutaneously with tubercle bacilli a variable number succumb to generalized tuberculosis in from three to eight weeks. Others may survive much longer. Practically all show involvement of the regional lymph nodes. In most animals the infection ultimately spreads to involve the spleen. If the dose of tubercle bacilli is large or if they are markedly virulent, or if the resistance of the particular animal is low, the spread of the tubercle bacilli will be more rapid and generalized. In these instances miliary involvement of the liver, spleen, kidneys, adrenals and other viscera may take place before the death of the animal. Pulmonary tuberculosis is relatively rare following the subcutaneous injection of tubercle bacilli.

Animals A, B, 1 and 2: All except the first of these controls were killed thirteen or more weeks after inoculation. Obviously the strain and dose of tubercle bacilli used in these experiments was not particularly virulent. At autopsy all animals showed caseated inguinal lymph nodes and tubercles in the spleen. Animals B and 2 also showed hepatic lesions. It should be stressed that animals 5, 6, 7 and 8 received but one-half the number of bacilli that were injected into the controls.

Animals 3 and 4: Following their inoculation with tubercle bacilli these animals were returned to their cages for two and one-half weeks before treatment was instituted. This period of time was allowed in order to insure fixation of the tubercle bacilli by the tissues. Shortly after treatment was started the animals began to lose weight, and thereafter they declined rapidly. Death occurred two weeks after the last treatment, or five weeks after their inoculation with tubercle bacilli. The immediate cause of their deaths was an acute, nontuberculous bronchopneumonia. More pertinent, however, were the following evidences of tuberculosis. The inguinal nodes were extensively caseated, and both animals showed miliary lesions of the spleen. In addition, animal 4 had large numbers of tubercles in the liver and several in the kidneys.

Animals 5 and 6: The preceding observations suggested that the tuberculous infection might have been too firmly established before treatment was given. Accordingly in animals 5 and 6 an interval of only ten days was allowed between the inoculation with tubercle bacilli and the institution of treatment. The administration of prontosil was continued for about two and a half weeks. One guinea pig (6) received two separate courses of treatment. These animals survived longer than did animals 3 and 4 (whose courses were probably abbreviated by the pneumonia), but they died eight and eleven weeks, respectively, after their inoculation with tubercle bacilli. Autopsies revealed that the tuberculosis had spread from the caseous inguinal lymph nodes to the spleen in both instances. In addition, viable tubercle bacilli were demonstrated in the inguinal nodes.

Animals 7 and 8: With the idea of bringing the drug in contact with the microörganisms before they were isolated by tissue reactions, these animals were given injections of prontosil for fourteen to sixteen days prior to their inoculation with tubercle bacilli. Treatment was continued for five days after the animals were infected. Although there was little loss of weight both guinea pigs developed enlarged inguinal nodes which ultimately broke down. Pig 7 was given an additional two weeks' course of treatment, and then both animals were sacrificed about seven weeks after the inoculation with tubercle bacilli. At autopsy both animals showed very extensive tuberculosis and it was evident that the administration of prontosil previous to the inoculation with tubercle bacilli in no way inhibited the multiplication or spread of the microörganisms.

COMMENT

From the observations on animals 3, 4, 5 and 6 it was apparent that relatively large doses of prontosil did not eradicate the tuberculosis, nor halt its spread in infected guinea pigs. The untreated animals lived much longer than did those that received prontosil. Although one is thereby tempted to ascribe a deleterious effect to the action of prontosil in the presence of tuberculous infection, such an assumption is not yet justified. The number of observations is too small to warrant any conclusion on this point, for the duration of life in experimental tuberculosis is markedly variable. Certainly, however, we may view with some concern the early demise of the treated animals in even this small series.

As has been suggested previously the pathology of tuberculosis offers an excellent reason why, even if one possessed an agent strongly bactericidal for the tubercle bacillus *in vitro*, the bacilli might be unaffected in experimental and clinical infections. The question then arises whether tubercle bacilli unprotected by avascular tissue and necrotic material would be affected by prontosil. The experiments with animals 7 and 8 were planned in an attempt to answer this question. The tissues of the animals were saturated with prontosil before the inoculation with tubercle bacilli. If the drug (or the products of its reduction in the body) were bactericidal for tubercle bacilli, then the microörganisms should succumb to it under the conditions of the experiment. The prontosil came in intimate contact with them before the bacilli had been fixed by protective tissue reactions. However, the regional lymph nodes became involved at least as rapidly as in the control animals, and autopsies showed the spread of the tuberculous infection to the abdominal viscera. There was then no evidence that the prontosil inhibited the growth or spread of tubercle bacilli, even though it came in contact with them before they were fixed in the tissues.

SUMMARY

1. Prontosil exerted no favorable influence on the course of experimental tuberculous infection in five guinea pigs.

2. In two other instances, the spread of tubercle bacilli was not inhibited by treating the animals with prontosil prior to their inoculation with the microörganisms.

3. In this small series the treated animals died much sooner than did the untreated controls.

CONCLUSIONS

No drug should be adopted or abandoned on the basis of a few observations. Because of the results in this small series of experiments, however, prontosil and related chemotherapeutic agents should not be given a trial in clinical tuberculosis until a significantly large and carefully controlled mass of experimental data clearly indicates the safety of such a trial.

The attention of the reader is directed to the paper by ARNOLD R. RICH AND RICHARD H. FOLLIS, JR.: The Inhibitory Effect of Sulfanilamide on the Development of Experimental Tuberculosis in the Guinea Pig, Bull. Johns Hopkins Hosp., 1938, *62*, 77, which was published since the receipt of this paper. (Editor)

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INFLUENCES OF MYCETES ON TUBERCLE BACILLI[1]

A Preliminary Report

D. BARGLOWSKI[2]

The behavior of various microörganisms living together in the same medium, or the influence they or their metabolic products produce on one another, may become apparent in different ways. Fundamentally we may expect three possibilities. First, the microbes may grow together without reacting on each other; second, they may have a fostering influence on each other (symbiosis); or finally, they may have a checking effect on one another (antagonism). For all three possibilities there may be found instances in human pathology and physiology as well as a great deal of research work which cannot be discussed here.

A number of authors have investigated particularly the action of mycetes on tubercle bacilli (Vaudremer, Manca, Borsotti, Schachsuwarly and Woldrich, Weissfeiler, Graef, Proca, etc.). The results reported by these authors are somewhat controversial. Some of them, however, are so far-reaching that confirmation by renewed investigation seems to be of great importance, both from the scientific and practical point of view.

The following brief summary is the report on a number of investigations which for technical reasons are partly based on only one or two series of experiments. We, therefore, can consider them only as a preliminary guide for more detailed work.

EFFECT OF FILTRATES FROM MYCETE CULTURES ON THE GROWTH OF ACID-FAST BACILLI

In this first experimental series ten strains of *Mycotorula albicans* related to each other and two strains of *Saccharomyces cerevisiae* were used in order to investigate the effect of their filtrates, when added to fluid culture medium. The results may be summarized as follows:

(*1*) The filtrates of eight mycetes, when added to Sauton's fluid in a concentration of 50 per cent, suppress the growth of the bovine tubercle

[1] From the Institute Carlo Forlanini and Clinics for Tuberculosis of the University of Rome, Professor Morelli, President.

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strain Vallée completely or almost completely. The filtrate of one of the mycetes (R7) showed a complete check until the fifth week after seeding, but from the fifth to the eighth week a thick and wrinkled cover developed, occupying approximately half of the surface of the medium, and resembling the growth of a human strain rather than that of a typical bovine Vallée culture. This is possibly due to the formation of a specially resistant form. In the growth in the flasks containing 25 per cent filtrate, there was no attenuation at all, but rather an increase, as compared with its growth in pure Sauton's fluid; this was considerable after the first week and remained clearly so for three to five weeks; later on the difference disappeared. Heating the filtrates for half an hour at 56°C. did not change the effect.

(*2*) The retarding effect of mycete filtrates on timothy bacillus is generally slighter. But here also some filtrates (50 per cent) impeded the growth; this was, however, in several cases only a transient phenomenon which disappeared after two and three weeks, respectively. No suppression of growth occurred when 25 per cent of filtrate was added. In this case also heating at 56°C. did not alter the result.

(*3*) The results with strains of human origin are not unequivocal. Generally the checking influence in this group is much slighter than that observed with the bovine strain Vallée.

THE GROWTH OF TUBERCLE BACILLI ON SOLID CULTURE MEDIA FOLLOWING SUSPENSION IN FILTRATES

Human tubercle bacilli (strain H522) were suspended in filtrates of several mycetes; 4, 24, 72 and 96 hours later, one loopful of each suspension was seeded on Petragnani medium. The results were somewhat contradictory, but we may conclude that the vitality of the bacilli in 50 per cent filtrate may be reduced within a short time. This also occurs in the less concentrated solutions after 96 hours, so that the growth on solid culture media either sets in several days later or does not develop at all.

EXPERIMENTS ON "FORCED ANTAGONISM" OF MYCETES AND TUBERCLE BACILLI

In a series of articles, Schiller describes the phenomenon of "forced antagonism." If, in a nitrogen free medium, bacteria with proteolytic properties (for example, *Bacillus mesentericus*) were brought in contact with germs not producing proteolytic substances, the latter were digested

and dissolved. Thus streptococci are dissolved by *Bacillus mesentericus* (first report). In some further articles (fourth, fifth, seventh communication) Schiller reports also on forced antagonism of yeasts on tubercle bacilli. His procedure is as follows: "Two beer-yeast-agar cultures are suspended in 2 cc. of a 2 per cent solution of saccharose and 0.1 mg. of tubercle bacilli is added to the emulsion." At a microscopical examination after forty-eight hours the yeast shows intense budding. The tubercle bacilli show thin, slightly stained threads or finely granulated formations. They are not numerous, however. Blue patches are to be met with, which, on careful examination, prove to consist of fine granules, the remains of the tubercle bacilli. On adding a few drops of broth, fermentation sets in again, and the bacteria are completely digested (fourth communication).

We have carefully followed Schiller's directions in our experiments. But the microscopical investigation alone did not seem sufficient to us. We, therefore, also made cultures from the emulsions on solid media. One platinum loopful was seeded on each of four Petragnani slants after 1–2, 24, 48 and 96 hours, respectively. Three *Mycotorula* strains and one *Saccharomyces* strain were employed.

In suspensions with *Saccharomyces* the culture results were at once obvious; no suppression of growth was found.

In suspensions with *Mycotorula* strains a judgment was rather difficult, since both mycetes and tubercle bacilli grew. Many colonies were obviously either mycetes or tubercle bacilli, but a great many others could not be recognized. Only on examination of a large number of microscopical smears and by macroscopical investigation of the colonies with the aid of the megascope,[3] a fairly reliable differentiation was obtained. Besides pure colonies of tubercle bacilli or of mycetes, there were regular mixed colonies. In the majority of the cases the relation of mycetes to tubercule bacilli was the same in each of the four test tubes belonging together, that is, sometimes showing both microbes growing in almost identical number, at another time one kind predominating. We shall not discuss the meaning of these differences, since the following deductions will show how problematic the results are, and how careful one has to be as to the conclusions when such a coarse method is used. We were struck by the following fact: in a microscopical investigation of the colonies of several test tubes we found tubercle bacilli

[3] Designed by the firm of Fratelli Koristka, Milan.

and mycetes lying together. When the same test tubes were examined four weeks later we only saw mycetes colonies (also microscopically) and, as it were, in opposition to the other grayish, greasy and brittle mycetes colonies, they made the impression of a gray, rather coarse and tough cover, some material of which could hardly be taken out. When attempts were made at getting hold of such a colony *in toto*, in order to examine the bottom of it microscopically, we were surprised to find under the mycetes colonies well preserved typical colonies of tubercle bacilli, consisting of small acid-fast rods. The same was found in many other test tubes. But also the reverse could be observed. In several cases, the growth began as soon as three to five days after seeding, and nearly the whole culture medium was covered with fine colorless spots, which were microscopically mycetes. At an examination seven weeks later, only a few colonies of mycetes were found, scarce mixed colonies and many tubercle bacilli colonies. The fact that there were only so few pure colonies of mycetes, is in my opinion due to a luxuriant growth of tubercle bacilli superseding the mycetes.

MICROSCOPICAL STUDIES

Tubercle bacilli in mixtures of Sauton's fluid and filtrates: The microscopical findings confirm on the whole the results of the cultures. Those filtrates which had a suppressing effect on the growth of tubercle bacilli caused not infrequently a decrease in acid-fastness; in a few cases also degenerated forms and non-acid-fast forms were found. These findings however are apparently due to the age of the cultures. If specimens are examined after eight weeks and the original culture was three to four weeks old, we actually deal with the original culture pellicle, which has survived in an unfavorable culture medium for two to three months. It is well known that we are likely to find non-acid-fast or degenerated forms under such circumstances. These were also met with in suspensions of tubercle bacilli kept for a longer period in media poor in nutritive materials (Barglowski); thus decreased acid-fastness is not proved to be due to the action of the filtrates.

Cultures of tubercle bacilli suspended for some time in filtrates almost invariably showed normal acid-fastness.

Tubercle bacilli in the so called "forced antagonism": Contrary to Schiller's statement, in the mixed suspensions of mycetes and tubercle bacilli, no suppression of tubercle bacilli could be observed. In the cultures made from these suspensions were found (*1*) pure colonies of

mycetes, (*2*) pure colonies of tubercle bacilli and (*3*) mixed colonies, in which the two kinds of germs were growing together in different layers. This may be an analogon to the finding already mentioned, that a pellicle of mycetes had regularly outgrown the colony of tubercle bacilli. In other cases the tubercle bacilli filled the network of the mycelia, so that one might suppose that the two kinds of germs are in symbiosis. In some smears we found polymorphus forms of tubercle bacilli.

Regarding our experiments as preliminary ones, we have omitted all technical details, tables and figures, which we hope to be able to publish after having done more extensive investigations. For the same reason we shall not discuss the results in detail.

It seems important that the same filtrate checks in a 50 per cent concentration, but never in a 25 per cent concentration, where perhaps it even shows a slight increase in some cases. Perhaps this result can explain the contradictions in the publications of different authors.

The experiments with mixed cultures of mycetes and tubercle bacilli showed that in these cultures the colonies, which even after microscopical examination were thought to be mycetes colonies, proved to be mycetes pellicles covering colonies of tubercle bacilli, consisting of well preserved, typical acid-fast rods.

I wish to acknowledge my indebtedness to Professor Besta for his valuable suggestions and kind assistance during the whole course of my work.

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MOLECULAR WEIGHT, ELECTROCHEMICAL AND BIOLOGICAL PROPERTIES OF TUBERCULIN PROTEIN AND POLYSACCHARIDE MOLECULES[1,2,3,4]

FLORENCE B. SEIBERT,[5] KAI O. PEDERSEN AND ARNE TISELIUS

It is of fundamental importance to obtain as nearly complete an understanding as possible of the size and other physical properties of the molecule or molecules in tuberculin which are able to elicit the tuberculin reaction. Not only is such knowledge of great value in the preparation of a pure product and in further attempts to explain the cause of the tuberculin reaction itself and its relationship to the disease, but also it will be helpful in interpreting a whole series of similar immunological reactions of which this is a prototype. The differences observed between tuberculin reactions (the delayed type of reaction) and typical protein sensitization reactions (the immediate type) may well depend upon some physical property of the molecule, and both are obviously elicited by constituents in the culture filtrates from tubercle bacilli.

Throughout this study, therefore, the relationship in various preparations between tuberculin potency and antigenicity, on the one hand, and molecular size or shape and electrochemical properties, on the other, was noted, and the aim was to prepare homogeneous fractions having certain of those different properties. The molecular homogeneity of the fractions was determined in different ways. For example, in the first place the rate at which the molecules sedimented, which in turn is dependent upon their molecular weights, was determined in the Svedberg ultracentrifuge (1), rotating at a velocity of 60,000 to 70,000 r.p.m. and giving centrifugal forces of 285,000 to 360,000 times gravity. The

[1] Presented at a session of the Pathological Section at the 34th annual meeting of the National Tuberculosis Association, Los Angeles, California, June 22, 1938.

[2] From the Institute of Physical Chemistry of the University of Upsala, Sweden, and the Henry Phipps Institute of the University of Pennsylvania, Philadelphia, Pennsylvania.

[3] Aided by grants from the Committee on Medical Research of the National Tuberculosis Association, and from the Anderson, The Rockefeller and the Wallenberg Foundations.

[4] A more comprehensive paper giving experimental details is to be found in the Journal of Experimental Medicine, September, 1938.

[5] John Simon Guggenheim Fellow, 1937–1938.

refractive index scale method was used for determining the concentration gradient in different parts of the cell during the sedimentation, and from this could be calculated the sedimentation constant (1). The type (that is, the degree of symmetry) of the curves obtained in the resulting diagrams furnished the first indication of the degree of homogeneity of the molecules.

Some idea of the molecular homogeneity could also be obtained from determinations of the rate of diffusion, using the special cell and refractive index scale method developed by Lamm (2). When this diffusion constant for an apparently homogeneous molecule was known, together with the sedimentation constant as described above, the molecular weight could be calculated from the formula given by Svedberg (3), $M = \frac{RTs}{(1 - V\rho)} D$, where R is the gas constant, T the absolute temperature, ρ the density of the solution and V the specific volume.

These two methods, therefore, furnished strong evidence of the homogeneity of a fraction, but a further criterion could be gained by comparing the diffusion constant so obtained with one calculated from the sedimentation curves. A deviation between the two would indicate heterogeneity.

Molecular weight homogeneity could be judged, therefore, from the rates of sedimentation and diffusion, but in some cases, such as the serum globulins, which were found to be homogeneous from these viewpoints, further studies on electrophoretic migration showed inhomogeneity (4). Likewise there have been cases of inhomogeneous sedimentation and diffusion, but homogeneous electrophoresis (for example, dissociation of proteins into particles of nearly unchanged chemical nature). Therefore in addition to sedimentation and diffusion determinations studies were made on the tuberculin preparations with the Tiselius (4) electrophoresis apparatus. The criterion for electrochemical homogeneity was limited to observations of the number of individual boundaries migrating, as representative of separate components, and not to the purity of the individual boundaries.

Chemical analyses on the various fractions were made as follows: total concentration by means of the dipping refractometer, nitrogen by a modification of the micro-kjeldahl method of Pregl, polysaccharide by the orcin-sulphuric acid method of Tillmans and Philippi (5) or the carbazol reaction of Dische (6), nucleic acid by the method of Dische (6), potency by means of the intracutaneous skin test in tuberculous guinea

pigs, toxicity by means of the lethal test, and precipitin tests to the protein fractions with rabbit antiserum and to the polysaccharide with horse antiserum.

Studies on original untreated tuberculin medium filtrates (human PN and H37, or bovine (no. 523)) showed that they contained from 25 to 57 per cent polysaccharide. In all cases the sedimentation diagrams gave evidence of only one main component (see table 1), but the asymmetry of the curves which developed as sedimentation progressed indicated that there were some smaller and larger molecules present. When tested in the unpreserved state or preserved with 0.5 per cent phenol or 1:10,000 "merthiolate,"[6] there was very little difference except that slightly more of the quickly sedimenting components, probably denatured protein, were present in the preserved specimens.

TABLE 1

Sedimentation of culture filtrates

SUBSTANCE	PER CENT OF TOTAL AS POLYSACCHARIDE	$S_{20} \times 10^{13}$
TPU—Human (PN)—unpreserved		1.7
+0.5% phenol		1.7
+"merthiolate" (1:10,000)	35.7	1.8
TPU—Human (H37)	72.5	1.8
TPU—Bovine (no. 523)	32.1	1.7
TPU—Timothy (Moeller)	26.8	1.4 1.6

Electrophoretic studies of these original tuberculins, however, showed the presence of several components, two or three of them being protein constituents migrating toward the positive pole at pH 8.0 and one a polysaccharide component with no mobility. Because of the difference in mobilities of these components it was therefore possible to separate the protein and polysaccharide by repeated electrophoresis.

In the case of the bovine type bacillus tuberculin a very satisfactory separation resulted, so that the final solution showed but one boundary in electrophoresis and in sedimentation. The sedimentation and diffusion diagrams indicated a single homogeneous substance. Assuming the specific volume to be the same as for the human type bacillus tuberculin protein, a molecular weight of 10,000, was calculated (see table 2).

On the other hand, the human bacillus tuberculin and timothy bacillus

[6] Product of Eli Lilly and Company.

fractions obtained in electrophoresis, both showed the presence of two components. The latter, however, gave on sedimentation only one main gradient, but it was markedly heterogeneous. The human type tuberculin, when run in the centrifuge, showed the presence of two clearly defined components, with $S_{20} = 1.9$ and 4.9.

Biological tests on tuberculous guinea pigs (skin and toxicity) with the fractions of the human type tuberculin obtained by electrophoresis indicated that the protein fraction most closely associated with the carbohydrate may be somewhat more potent and toxic than the separated protein, but further confirmation of this result would be necessary to establish its significance.

The increased toxicity, however, was not due to a toxic carbohydrate, as indicated by the fact that as much as 10 mg. of the polysaccharide, isolated in this way in its most native form, was not toxic. Furthermore, previous studies (7) on the polysaccharide isolated in quantity by chemical methods showed that even as much as 50 mg. given intraperitoneally did not kill tuberculous guinea pigs.

The carbohydrate fraction isolated in electrophoresis apparently was immobile, and therefore neutral from an electrochemical standpoint, and when analyzed in the ultracentrifuge was found to have one main gradient and a very small amount of a larger molecule, probably protein (see table 2). The tuberculin polysaccharide which had been isolated by chemical means was then studied and appeared to be entirely homogeneous on sedimentation at various concentrations, and was homogeneous in diffusion. Its specific volume was 0.619 and therefore the molecular weight proved to be about 9,000. It apparently differs remarkably from all polysaccharides previously studied in being homogeneous. The precipitin titre for antiserum against tubercle bacilli was the same for the polysaccharide whether it was isolated in electrophoresis or by chemical procedure.

Attempts were then made to isolate a homogeneous fraction from human tuberculin by chemical methods, but most of the many fractionations yielded heterogeneous products. Only one method proved to be satisfactory; this consisted in first removing a denatured fraction by bringing a half-saturated ammonium sulphate fraction to pH 4.6–4.8 with acetate buffer, and then isolating the homogeneous fraction (TPA-30b) by reprecipitation for at least four times at one-tenth to one-fourth saturation with ammonium sulphate. Such a fraction was made four different times, and when tested in the centrifuge and for diffusion gave

symmetrical curves (see table 2). The specific volume was 0.700 and therefore a molecular weight of 32,000 was calculated. This fraction had only 2 per cent polysaccharide, and neither freezing at −8° to −10°C. nor drying *in vacuo* altered the sedimentation characteristics. It was found also to have a single boundary in electrophoresis and the isoelectric point was at pH 4.3. When titrated electrometrically with the glass electrode the isoionic point was found to be at pH 4.7.

This fraction, furthermore, gave a high precipitin titre with antiserum to the whole mixed protein fraction, and, when tested intracutaneously in tuberculous guinea pigs, caused their death with an exceptionally

TABLE 2

Homogeneous molecules isolated from tuberculin

SUBSTANCE	M MOLECULAR WEIGHT	$S_{20} \times 10^{13}$	$D_{20} \times 10^{7}$ (FOUND IN DIFFUSION)	$D_{20} \times 10^{7}$ (APPARENT, CALCULATED FROM SEDIMENTATION DIAGRAMS)	f/fo	PER CENT OF TOTAL AS POLYSACCHARIDE	PER CENT OF TOTAL AS NUCLEIC ACID
Tuberculin polysaccharide (by electrophoresis)		1.8					
(by chemical isolation)	9,000	1.6	11.0	13.5	1.5	100.0	0
Bovine (no. 523) protein	10,000	1.6	12.0	11.5	1.3	4.7	
TPA—30 b (Human)	32,000	3.3	8.2		1.2	3.1	0
TTPA-A (Timothy)	17,000	1.8	10.2	13.6	1.2		
PPD-b2	*	1.5	2.1	14.5	*	9.6	5.7
PPD-b3	16,000	1.2	6.7	11.1	1.9	4.4	3.0
PPD-b3b	9,000	1.0	10.0	10.3	1.6	1.2	1.6

* These values have not been calculated since their significance would be doubtful on account of inhomogeneity and sedimentation and diffusion anomalies.

small dose, or gave a surprising demonstration of the local anaphylactic type of reaction with 0.05 mg. Four out of nine guinea pigs were dead twenty-four hours after the intracutaneous test with a total of 0.25 mg. or less of the tuberculin fractions, and in those surviving there were very large, diffuse and deep reddish or purple local reactions, in contrast to a small and more localized typical tuberculin reaction to a PPD fraction given simultaneously. At forty-eight hours the relative sizes of the two reactions were reversed and the typical delayed reaction with the PPD fraction was the larger of the two, and the reddish and purple character of the former had disappeared.

The protein from the timothy bacillus was also finally obtained in

homogeneous form (TTPA-A) by ammonium sulphate (0.25 saturation) precipitation at pH 3.0. The specific volume was 0.748, and therefore, as given in table 2, the molecular weight was 17,000.

Attempts were then made to obtain the smallest potent tuberculin molecule. This was thought to be the nonantigenic PPD (8). An investigation of the PPD, however, showed that it was not homogeneous in sedimentation and that it contained 22 per cent nucleic acid. In electrophoresis it showed the presence of polysaccharide, as evidenced by an immobile boundary, and two other components which migrated to the positive pole with an extremely high mobility. On further study it was found that this high mobility was due to the presence of nucleic acid, since the nucleic acid of the tubercle bacillus itself had a high mobility and as methods were applied to remove the nucleic acid from the PPD fractions their mobilities correspondingly decreased.

Finally, purification of the PPD was most successfully obtained by a fractional precipitation with hydrochloric acid using the hydrogen electrode. That fraction, PPD-b2, removed at pH 4.0, proved to be abnormal in its reactions on sedimentation and diffusion and showed a marked tendency toward gel formation.

After this fraction was removed, another one was obtained by precipitation with trichloracetic acid. This fraction, PPD-b3, was further purified by electrodialysis, and proved to be as nearly homogeneous as it has so far been possible to obtain the small molecule. This fraction had only 3 per cent nucleic acid and the molecular weight was calculated to be about 16,000 (see table 2). Since a diffusion constant of 6.7 is abnormally low for a molecule with $S_{20} = 1.2$, the molar frictional ratio f/fo (see table 2) was calculated (1(b)). This ratio was found to be 1.9, which is far from unity, indicating that the molecule either deviated considerably from the compact spherical shape or that it was hydrated. Therefore, Doctor Snellman, of the Institute of Physical Chemistry at Upsala, kindly made a determination for us on this preparation by means of the method of double refraction in flow. He found a marked effect, indicating very asymmetrical shape. It is probably, therefore, a considerably stretched rather than a spherical molecule. Furthermore, attempts to determine the isoelectric point were unsuccessful because a precipitate occurred when the solution became more acid than pH 4.36, but the character of the curve obtained on the alkaline side indicated that the molecule bound more base than did the large antigenic molecule, and, therefore, probably had more polar groups. This finding also is

consistent with the idea that the molecule is stretched. In such elongated molecules, where extra polar groups are exposed, an aggregation of the molecules may easily take place through these exposed groups, as found by Astbury, Dickinson and Bailey (9) in their X-ray studies of heated egg albumin. Such a phenomenon probably explains the gel-like particles found in the case of PPD-b2.

Since the most probable molecular weight of PPD-b3 is about 16,000, or probably approximately the same as found for the molecules in the original medium which are antigenic, it would seem likely that the loss in its antigenicity may be due to a distortion or change in configuration of the molecule rather than or as well as to a disaggregation into smaller units. Moreover, in view of the fact that adsorption to aluminum hydroxide or charcoal renders the nonantigenic molecule antigenic (10), it is probable that some change in physical property rather than the presence of a special constituent is responsible for the antigenic properties.

During the electrodialysis used to purify the PPD-b3 a fraction, PPD-b3b, passed through the membrane to the cathode, and it was recovered by precipitation with trichloracetic acid. It proved to be a very interesting substance, since it gave all the protein reactions, was considerably less potent in eliciting the tuberculin reaction, and was molecularly homogeneous with a weight of 9,000 (see table 2).

We acknowledge our sincere gratitude to Professor The Svedberg for his kind interest and generous extension of the excellent facilities of his laboratory, and express our thanks to the members of his staff for their hospitable assistance.

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THE INCIDENCE AND CONTROL OF TUBERCULOSIS IN HIGH SCHOOL CHILDREN[1]

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The importance of early diagnosis of pulmonary tuberculosis has been repeatedly emphasized, and an intensive educational campaign has made the medical profession and the public familiar with the symptoms that indicate the clinical onset of the disease. As a result, a physician is consulted in most instances soon after ill health is noted, and with more general application of fluoroscopy and X-ray film examination delay in diagnosis is considerably less common. Nevertheless, even when a diagnosis is made with reasonable promptness a majority of patients are found to have moderately advanced or far advanced disease, for tuberculous lesions commonly progress to these stages before causing definite, persistent symptoms. It is now widely recognized that before symptoms develop there is a period of months or years during which the lesion could be detected in a latent or asymptomatic form by X-ray examination.

The "survey" method of case-finding is the application of X-ray examination to groups not selected because of known contact, exposure to tuberculosis being revealed by a positive tuberculin reaction. The groups most frequently selected for examination have been student nurses, university men and women, industrial employees, and, especially, public school children. Case-finding programs have been instituted in the public schools in many sections of the country, largely because school children are readily accessible, and because funds for the protection of children from tuberculosis are more easily obtainable. Often, for these reasons and because of the larger number of children in elementary schools, examinations have been chiefly confined to younger children.

In programs in which the proportion of preadolescent children is high, the number of significant tuberculous lesions discovered has been so small that the practical value of the survey method in tuberculosis control has been seriously questioned. The tuberculous lesions commonly found in preadolescent children are foci in the lungs or tracheobronchial

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lymph nodes that have undergone calcification. We are convinced by previous studies that calcified lesions of childhood type do not result in the development of adult tuberculosis. They are significant only as an indication of prolonged exposure to tubercle bacilli which, if continued into adolescence, may result in serious adult-type disease. Unless facilities are equal to the task of examining intimate associates of the children with calcified lesions, the discovery of such lesions is largely of epidemiological interest. It is neither necessary nor feasible to recommend treatment for these children.

The incidence of clinically significant tuberculous infiltrations in preadolescent children is extremely small. In a recent survey of a boys' school situated in an industrial town in Pennsylvania, no instance of a tuberculous lesion that could be considered of clinical significance was found on X-ray examination in 495 children between the ages of 7 and 13 years. Increasing recognition that the examination of preadolescent children is not a profitable field for the expenditure of public funds is indicated by the constantly growing popularity of tuberculosis case-finding programs in high schools. Numerous surveys have been reported in the literature during the past decade and many cities have instituted permanent programs for the detection of tuberculosis in high school students.

A case-finding program employing the tuberculin test and X-ray examination was begun in the public schools in Philadelphia in 1924. With the discovery that the incidence of significant lesions in elementary school children was very small, studies were instituted in the high schools in 1927. Results of these examinations were reported in 1929 (1) and in 1934 (2). In the first part of the present paper we are reporting the results of additional examinations with a discussion of the changes that have occurred since the beginning of the program in 1927. In the second part the methods of tuberculosis case-finding in high schools and their value in the antituberculosis campaign are discussed.

PART 1

RESULTS OF EXAMINATIONS FROM 1931 TO 1934

X-ray examination with stereoscopic films was given to 8,018 students between 1931 and 1934. These students were divided into four groups, namely high school pupils, trade school pupils, students at the municipal teachers' training school and applicants for admission to the latter.

Consent of parents was required for examination of high school and trade school pupils, but examination of the other two groups was compulsory. The tuberculin test was not employed.

The high school group consisted of 6,264 pupils from ten of the eleven high schools in Philadelphia and included children from all social and

TABLE 1

Results of X-ray examination of 6,264 high school students 1931–1934

AGE	NUMBER EXAMINED	TUBERCULOUS LESIONS OF CHILDHOOD TYPE			TUBERCULOUS LESIONS OF ADULT TYPE			
		Calcified node or nodule	Uncalcified node or nodule	Pulmonary infiltration	Total adult type lesions	Grade 1*	Grade 2*	Grade 3*
Boys								
years								
13	14	3						
14	126	16		2				
15	388	46	2		2(0.5%)			2
16	730	86		7	8(1.1%)	7		1
17	827	106	7	5	23(2.8%)	10	2	11
18	360	56	2	2	9(2.5%)	3	2	4
19	102	9	1		5(4.9%)	3		2
20	25	3		1	2(8.0%)	1		1
	2,572	325(12.7%)	12(0.5%)	17(0.7%)	49(1.9%)	24(0.9%)	4(0.2%)	21(0.8%)
Girls								
13	12						0	
14	108	17	1	1	1(0.9%)		0	1
15	592	69	1	3	11(1.9%)	4	2	5
16	1,281	166	1	3	38(3.0%)	16	6	16
17	1,199	144	6	7	33(2.8%)	21	5	7
18	417	57	1	1	26(6.2%)	11	7	8
19	73	11	1		3(4.1%)	2		1
20	10	1			1(10.0%)	1		
	3,692	465(12.6%)	11(0.3%)	15(0.4%)	113(3.1%)	55(1.5%)	20(0.5%)	38(1.0%)

* Description of lesions included in grades 1, 2 and 3 is found on page 415.

economic classes. Negroes constituted 7.4 per cent of the children examined. The results of X-ray examination are shown in table 1. In these adolescent children no significant variation with age occurred in the incidence of calcified lesions. Of 3,251 students between 13 and 16 years, 403, or 12.4 per cent, had calcified primary tuberculous lesions, while 387, or 12.8 per cent, of 3,013 students between 17 and 20 years

TABLE 2

Results of X-ray examination of adolescent groups in Philadelphia, 1927–1937

	SEX	NUMBER EXAMINED	AVERAGE AGE	TUBERCULOUS LESIONS OF CHILDHOOD TYPE			TUBERCULOUS LESIONS OF ADULT TYPE			
				Calcified node or nodule	Uncalcified node or nodule	Pulmonary infiltration	Total adult type lesions	Grade 1*	Grade 2*	Grade 3*
			years							
High schools 1927–28	M	722	15.7	134(18.6%)		11(1.5%)	10(1.4%)	4(0.6%)	4(0.6%)	2(0.3%)
	F	527	15.6	119(22.6%)		8(1.5%)	14(2.7%)	7(1.3%)	2(0.4%)	5(1.0%)
High schools 1931–34	M	2,572	16.5	325(12.7%)	12(0.5%)	17(0.7%)	49(1.9%)	24(0.9%)	4(0.2%)	21(0.8%)
	F	3,692	16.4	465(12.6%)	11(0.3%)	14(0.4%)	113(3.1%)	55(1.5%)	20(0.5%)	38(1.0%)
Trade school 1931	F	470	15.0	53(11.3%)		3(0.6%)	6(1.2%)	3(0.6%)	2(0.4%)	1(0.2%)
Teachers' training college 1931	M	74	18.3	13(17.6%)			4(5.4%)	1	2	1
	F	444	18.4	49(11.0%)	2(0.5%)	4(0.9%)	25(5.6%)	12(2.7%)	5(1.1%)	8(1.8%)
Applicants for teachers' training college 1932–34	M	230	17.4	28(12.2%)	6(2.6%)		5(2.2%)	4(1.7%)		1(0.4%)
	F	536	16.8	72(13.4%)	1(0.2%)	4(0.8%)	28(5.2%)	15(2.8%)	3(0.6%)	10(1.8%)
High school 1937	M	557	16.7	54(9.7%)		3(0.5%)	9(1.6%)	6(1.1%)	1(0.2%)	2(0.4%)
	F	691	16.2	64(9.3%)	1(0.1%)	1(0.1%)	20(2.9%)	9(1.3%)	4(0.6%)	7(1.0%)
Total		10,515		1,376(13.1%)	33(0.3%)	65(0.6%)	283(2.7%)	140(1.3%)	47(0.4%)	96(0.9%)

* Description of lesions included in grades 1, 2 and 3 is found on page 415.

had similar lesions. Nonapical infiltrations of childhood type occurred in 17, or 0.7 per cent of boys, and in 14, or 0.4 per cent of girls. These infiltrations were for the most part wholly strandlike and presumably inactive. There was no apparent variation with age in their incidence.

In both boys and girls between the ages of 14 and 20 years there was an increase in the frequency of adult-type lesions with increase in age. At 15 years of age apical infiltrations were found in 1.3 per cent of 980 students, while at 18 years of age 4.6 per cent of 777 students had similar disease. Infiltrations which by extent and density suggested that they were probably already the cause of symptoms or physical signs occurred in 8, or 0.3 per cent of boys, and in 16, or 0.5 per cent of girls. Eleven of the 24 lesions were moderately advanced in extent and one was far advanced.

The trade school group consisted of 470 girls whose average age was 15.0 years. These students have not been included in the high school group because they were younger, and came from poorer families. The percentage of Negroes was much higher, namely, 15.1 per cent. The results of X-ray examination are shown in table 2. There were no moderately or far advanced lesions in this group.

High school students applying for admission to the municipal teachers' training college were required to have X-ray examination of the lungs. This group consisted as a rule of senior students of high scholastic ability, whose economic circumstances prevented payment of the fees usually necessary to procure a college education. Seven hundred and sixty-six students between the ages of 14 and 24 years were examined, of whom 5.2 per cent were Negroes. Two of the girls with adult-type tuberculosis had moderately advanced disease.

The entire student body of the municipal teachers' training college, consisting of 518 students between the ages of 15 and 24 years, was required to have X-ray examination in 1931. Negroes constituted 7.0 per cent of the group. One boy and one girl had moderately advanced disease.

RESULTS OF EXAMINATIONS IN 1937

Examinations employing the tuberculin test and X-ray films were offered in 1937 to the pupils of two high schools previously surveyed in 1927–1928 and reported (1) as schools E and F. The students of these two high schools come from a district ordinarily considered poor and

congested, but in which the death rate from tuberculosis does not differ appreciably from that of the city as a whole. Estimates available for 1930 and 1934 show that the school district had death rates from tuberculosis in the white population of 65.8 and 49.8 per 100,000 respectively, while in those years the corresponding rates for the city were 64.7 and 51.7 per 100,000. The pupils are in large part the children of foreign born parents; in 1927–1928 Jewish children constituted the largest racial group, while in 1937 the children of Italian parents formed the largest group. The proportion of Negroes was 4.9 per cent in 1927–1928 and 5.4 per cent in 1937. There had been no apparent change in the social and economic circumstances during the interval. Consent of parents was a prerequisite for examination in both years. In 1937 more children in the senior class accepted the opportunity for examination and as a result the average age was approximately eight months higher than in 1927.

The intracutaneous tuberculin test using three graded dosages of Old Tuberculin was used in 1927–1928, the maximum dosage being 1.0 mg. Children who failed to react to this quantity were considered tuberculin-negative. In 1937 Purified Protein Derivative was used. Children who failed to react to an initial injection of .000,02 mg. were reinjected at the end of 48 hours with .005 mg. Children who failed to react to .005 mg. of Purified Protein Derivative were considered tuberculin-negative. Numerous comparisons at the Henry Phipps Institute have shown that the two substances in the dosages employed give practically identical results (3).

Table 3 shows the incidence of positive tuberculin reactions in 1927–1928 and in 1937 for boys and girls from ages 12 to 20 years. There is no apparent explanation for the disproportionate decline in tuberculin reactors in girls between the two tests. The percentage of reactors in girls in 1927–1928, namely 89.9 per cent, is the highest obtained in our studies of high school students, but does not differ markedly from the percentages found in girls tested in other high schools in Philadelphia in 1928 and 1929, namely 81.4 per cent in school G (1) and 88.1 per cent in school J (2).

Table 4 shows the incidence of positive reactors in children of Italian and Jewish parentage and indicates that the incidence of positive reactions has declined in children of both racial groups. The incidence of reactions in Negro children remained practically unchanged, while the

incidence in a miscellaneous group including children of all other racial origins showed a decline similar to that seen in Italian and Jewish children.

The incidence of infection found in 1937, 68.0 per cent in boys and 61.9 per cent in girls, is higher than that reported in recent years from other American cities, and suggests that the sharp drop in the incidence

TABLE 3

Tuberculin reaction in high school students

1927–1928				1937			
Age	Number tested	Number positive	Per cent positive	Age	Number tested	Number positive	Per cent positive
High School E (Boys)							
years				*years*			
12	11	8					
13	51	35	68.6				
14	127	87	68.5				
15	210	163	77.6	15	2	1	
16	182	139	76.4	16	262	177	67.6
17	84	60	71.4	17	205	136	66.4
18	38	31	81.6	18	86	64	74.4
19	16	9		19	1	1	
20	3	3		20	1		
Average 15.4	722	535	74.1	16.7	557	379	68.0
High School F (Girls)							
12	3	3					
13	31	27	87.1				
14	75	67	89.4	14	11	5	
15	127	107	84.3	15	119	76	63.8
16	145	136	93.8	16	317	192	60.6
17	103	93	90.2	17	200	126	63.0
18	38	36	94.7	18	36	24	66.6
19	5	5		19	6	3	
				20	2	2	
Average 15.6	527	474	89.9	16.2	691	428	61.9

of tuberculous infection in Minneapolis (4) has not occurred in large Eastern cities.

RESULTS OF X-RAY EXAMINATIONS

In both surveys, namely in 1927–1928 and in 1937, an attempt was made to examine by X-ray all pupils who reacted to tuberculin. In

1927 four tuberculin-positive boys did not receive further examination, while in 1937 all tuberculin-positive boys received X-ray examination and, in addition, 27 whose reactions were doubtful. In 1928 all tuberculin-positive girls received X-ray examination, while in 1937 nine girls who gave positive tuberculin reactions did not receive X-ray examination. Seven girls whose reactions to tuberculin were doubtful received X-ray examination.

In the 1927–1928 survey, steroscopic films were made of each student and, in addition, an oblique film was taken with the intention of dis-

TABLE 4

Tuberculin reaction in Italian, Jewish and Negro students

	1927–1928			1937		
	Number tested	Average age	Per cent positive	Number tested	Average age	Per cent positive
Boys						
		years			*years*	
Italian	204	15.6	72.6	234	16.7	66.7
Jewish	439	15.2	72.8	231	16.6	69.3
Negro	31	16.0	77.4	11	17.0	81.8
All others	48	15.7	89.6	81	16.8	66.7
Total	722	15.4	74.1	557	16.7	68.0
Girls						
Italian	86	15.5	87.2	267	16.2	53.2
Jewish	346	15.6	89.9	249	16.1	65.0
Negro	30	16.3	93.3	56	16.6	85.7
All others	65	15.8	92.3	119	16.5	63.8
Total	527	15.6	89.9	691	16.2	61.9

covering calcified lesions of the tracheobronchial lymph nodes in the interbronchial angle and about the trachea. Retake films were made whenever a lesion, no matter how trivial, was suspected. In 1937 single films of the chest were taken, with stereoscopic retake films only when a significant lesion was suspected. No attempt was made to confirm by further examination the presence of suspected calcified lesions or scanty strandlike infiltrations of childhood type. A careful review of all films in both surveys was made in order to be sure that there was no inconsistency in interpretation. Revisions of diagnosis were made in a few instances. One girl, F-2, previously reported as having clinical tuber-

culosis, was excluded because, although her lesion was associated with a strongly positive tuberculin reaction and a calcified lesion of childhood type, it was bilateral and basal and hence probably nontuberculous. A boy, E-2, was also excluded for these reasons. Other revisions of diagnosis were of a minor character.

Table 5 shows the results of X-ray examinations. Percentages are based upon the total number who received the tuberculin test and not upon the number who received X-ray examination, because the incidence of significant tuberculous lesions occurring in apparently healthy tuber-

TABLE 5

Comparison of results of X-ray examination in 1927–1928 and 1937

	HIGH SCHOOL E		HIGH SCHOOL F	
	Boys		Girls	
	1927–1928	1937	1927–1928	1937
Average age	15.7	16.7	15.6	16.2
Total examined	722	557	527	691
Total X-rayed	531	406	474	419
Childhood type lesions:				
Calcified node or nodule	134(18.6%)	54(9.7%)	119(22.6%)	64(9.3%)
Uncalcified node or nodule	0	0	0	1(0.1%)
Pulmonary infiltrations	11(1.5%)	3(0.5%)	8(1.5%)	1(0.1%)
Adult type lesions:	10(1.4%)	9(1.6%)	14(2.7%)	20(2.9%)
Grade 1*	4(0.6%)	6(1.1%)	7(1.3%)	9(1.3%)
Grade 2*	4(0.6%)	1(0.2%)	2(0.4%)	4(0.6%)
Grade 3*	2(0.3%)	2(0.4%)	5(1.0%)	7(1.0%)

* Description of lesions included in grades 1, 2 and 3 is found on page 415.

culin-negative students in Philadelphia has proved very small and for practical purposes may be disregarded.

In our previous survey, 18.6 per cent of boys and 22.6 per cent of girls were found to have calcified densities of childhood type in lungs or lymph nodes, while in the present survey only 9.7 per cent of boys and 9.4 per cent of girls were found to have calcified densities of this nature. Similarly, 1.5 per cent of boys and 1.5 per cent of girls in the previous survey and 0.5 per cent of boys and 0.3 per cent of girls in the present survey were found to have childhood type infiltrations, chiefly strandlike lesions. The lower incidence of calcified and strandlike lesions of childhood type is, presumably, in large part due to the change from stereoscopic and oblique films and frequent reëxaminations in the previous survey to

single films, with no attempt to confirm the presence of suspected lesions of this type by reëxamination in the present survey.

These considerations do not, to any important degree, affect the comparison of incidence of adult-type infiltrations in 1927–1928 and 1937, for stereoscopic films were obtained for confirmation of almost every suspected lesion of this type. The results in the two surveys are almost identical; in boys, 1.4 per cent in 1927–1928 and 1.6 per cent in 1937 had apical infiltrations, and the incidence among girls was 2.7 per cent in 1927–1928 and 2.9 per cent in 1937.

For purposes of more accurate comparison the apical infiltrations have been subdivided, according to their roentgenological density, character and extent, into three groups designated as grades 1, 2 and 3. Grade 1 includes small infiltrations appearing as sharply defined strands or spots at the extreme apex, with salient shaped projections of irregularly thickened pleura. Although there may be doubt regarding the exact clinical significance of these minor lesions, there is ample pathological evidence that the appearance described represents adult-type tuberculosis which should not be disregarded in an epidemiological survey.

Grade 2 comprises more extensive infiltrations, usually of slight or moderate density, that are confined to the lung field above the clavicles and appear as grouped or confluent flocculent spots. Infiltrations of this character and extent, although very rarely producing symptoms or physical signs, not infrequently progress to clinical tuberculosis. Nevertheless, they are often overlooked or disregarded by roentgenologists whose experience is largely confined to interpretation of films showing the gross changes of advanced disease.

Grade 3 consists of more advanced apical lesions sufficiently extensive to appear below the clavicle. Scanty infiltrations appearing as scattered spots and strands are included, as well as denser lesions which, when encountered in patients with symptoms or physical signs, are designated as minimal, moderately advanced or far advanced tuberculosis. Although these students considered themselves in good health it was possible in some instances to obtain a history of symptoms which had been either disregarded or attributed to other causes. Physical signs, when present, were usually slight and indefinite. There was no instance of advanced disease in boys in either survey, but two girls in 1927–1928 and one girl in 1937 had moderately advanced tuberculosis.

It has been pointed out that the incidence of apical infiltrations did not decline between 1927–1928 and 1937. Subdivision of the lesions

according to their character and extent into grades 1, 2 and 3, as shown in table 5, indicates that there has been no appreciable change in the severity of the infiltrations. Approximately seventy per cent of the lesions found were small supraclavicular infiltrations belonging to grades 1 and 2, which may be disregarded by roentgenologists accustomed to advanced pulmonary changes. The more extensive infiltrations in grade 3 formed approximately thirty per cent of apical lesions. The proportions of grade 1, 2 and 3 lesions found among the students examined between 1931 and 1934 were similar, suggesting that this distribution is typical.

The close correspondence of the results of X-ray examination in 1927–1928, 1931–1934 and 1937 indicates that the high figures previously reported (1) cannot be attributed to the selection of schools in a congested district but must be considered representative of the situation throughout the city. The similarity of results, whether all students are X-rayed, as in 1931–1934, or whether only those reacting to tuberculin are X-rayed, as in 1927–1928 and 1937, supports the belief that the frequency of apical lesions in children who fail to react to tuberculin is very small and indicates that the practice in case-finding programs of omitting X-ray examination of those who fail to react to tuberculin is justified.

COMMENT

The findings reported have implications of pathological and epidemiological interest that may be briefly mentioned. It is widely believed that the reaction to tuberculin resulting from infection with tubercle bacilli persists for many years, and that in few instances the reaction changes from positive to negative. The percentage of reactors found in children in the first, second and third grades of elementary schools between 1927 and 1929 should indicate roughly the incidence of infection in the present group of high school students when they were 8 to 10 years younger. The studies of elementary school children indicated an incidence of infection in those grades of approximately 60 per cent. It is certain that many young children who failed to react to tuberculin ten years ago have acquired a positive reaction since that time. Since the present survey demonstrates an incidence of only 64.6 per cent in children with an average age of 16.4 years, it appears that during the past decade almost as many children have lost their ability to react to tuberculin in the dosages employed. The same conclusion is indicated by the results of Chadwick and Zack's survey of Framingham students in 1926

(5). The group aged 13 to 15 years in 1926 had an incidence of infection of 31 per cent, while in a study in 1917, nine years earlier, 39 per cent of children 4 to 6 years of age reacted to tuberculin. These observations suggest that changes in reaction from positive to negative may be by no means as uncommon as is generally believed.

It is usually accepted that the death rate from tuberculosis in a community is an index of the morbidity and thus of the opportunity of acquiring infection. Accordingly, a high incidence of infection would be expected in cities where the death rate from tuberculosis is high, and a low incidence of infection should be encountered in cities with a low tuberculosis death rate. A decline in the death rate should be accompanied by a roughly proportional decrease in the incidence of infection as determined by the tuberculin test.

TABLE 6

Relation of death rate from tuberculosis to incidence of tuberculous infection in children of high school age

CITY	YEAR	DEATH RATE PER 100,000 WHITE POPULATION*	PER CENT POSITIVE TO TUBERCULIN
Los Angeles	1936	83.0	43.7
Philadelphia	1927	68.3	80.8
New York	1930	62.0	67.3
Minneapolis	1926	87.7†	60.0
Philadelphia	1937	48.8	64.6
Detroit	1936	40.4	24.8‡
Minneapolis	1936	38.1†	22.2

* Inclusive of known deaths out of town of residents, except in Philadelphia where corrected figures are not available for 1927 and 1937. The correction necessary in Philadelphia is, however, less than 5 per cent.

† Death rates for total population. Figures not calculated for white population because of the small Negro population.

‡ Pirquet test employed.

Comparable data on death rates and incidence of infection are available in only a few instances. Results reported from several large American cities are presented in table 6. The incidence of infection in children of high school age is roughly proportional to the death rate in the community except in Los Angeles, where the incidence of reactors is disproportionately low. This may be due to the high proportion of students in Los Angeles who are newcomers and hence have not been long exposed to the greater opportunities for infection in that city, while

the death rate is presumably augmented by health seekers with advanced tuberculosis who quickly die of their disease, as well as by inclusion in the white groups of Mexicans in whom the death rate from tuberculosis is high.

In four cities observations on the decline in incidence of tuberculous infection have been reported. Beaven (10) analyzed the results of skin testing with 0.1 mg. OT routinely applied to children admitted to the Strong Memorial Hospital in Rochester. The incidence of reactors dropped from 14.8 per cent in 1926–1928 to 5.6 per cent in 1932–1934, while the death rate from tuberculosis in Rochester averaged 44 per thousand in the years 1926–1928 and 21 in the triennium 1932–1934. In Detroit, application of the Pirquet test to clinic children, for the most part in contact with known cases of tuberculosis, revealed 54 per cent reactors in 1930 and 26 per cent in 1936 (11). The death rate in Detroit declined from 82.7 to 52.5 per hundred thousand during the corresponding period. Unfortunately, these two studies embraced hospital and clinic children, and employed methods of tuberculin testing not accurately comparable.

Studies in Minneapolis employing 1.0 mg. of OT showed a decline of infection in children 12 to 15 years of age from 60 per cent in 1926 to 22.2 per cent in 1936, while comparable studies in slightly older children in Philadelphia revealed a drop from 80.8 per cent in 1927–1928, to 64.6 per cent in 1937. Comparison of the death rates from tuberculosis demonstrates a decline in Minneapolis from 87.7 per hundred thousand in 1926 to 38.1 per hundred thousand in 1936, while in Philadelphia the death rate in the white population fell from 68.3 in 1927 to 48.8 per hundred thousand in 1937.

The limited data available show the decline of tuberculous infection and mortality to be roughly proportional. The rapidity of decline observed in Minneapolis, Detroit and Rochester has not been paralleled in Philadelphia. It is noteworthy that while the present death rate in Minneapolis is relatively little lower than in Philadelphia, the percentage of adolescents reacting to tuberculin is markedly lower in Minneapolis, indicating that conditions in Philadelphia are more conducive to the spread of tuberculous infection.

Little study has been devoted to changes in the incidence of tuberculous lesions. Beaven, however, noted that whereas, in 1926–1928, 36.2 per cent of the children reacting to tuberculin showed X-ray or clinical evidence of tuberculous disease, in 1932–1934, there was evi-

dence of disease in 52.9 per cent of the reactors. Similarly, in Philadelphia we failed to detect a decline in the incidence of roentgenological lesions corresponding to the decline in the incidence of infection.

These results suggest the need of further study to define the relationship of incidence of infection to morbidity as well as to mortality in tuberculosis. It should not be assumed that they will decline proportionally.

PART 2

The widespread interest in the problem of tuberculosis control in high school children is indicated by the response to a questionnaire sent to school and health officials in thirty of the largest cities in the United States in November, 1936. Replies were received from 23 cities and almost without exception a keen interest in the problem was shown. Only eight cities were reported to be without a specific case-finding program in the high schools, and even in a number of these cities special emphasis was placed on the detection of tuberculosis in the routine physical examination of the students. Thirteen cities employed X-ray examination to detect tuberculosis in high school children, and in two other cities programs of this type were about to be instituted. Further evidence of the widespread application of case-finding methods in high school children is shown by numerous surveys that have been reported during the past decade from smaller cities, towns, and rural areas in many parts of the country. It seems desirable to review the methods employed and the results reported in the light of our experience in Philadelphia.

SELECTION FOR EXAMINATION

Due to limitation of facilities and to the expenditures involved, it is rarely possible to offer examinations to all the high school children of a community. It is desirable, therefore, to select for examination those groups in which the number of children with tuberculous lesions should be largest. It is recognized that the incidence of tuberculous lesions in adolescent children increases with age, and at each age is considerably higher in girls than in boys. From the standpoint of public health, detection of a single case of tuberculosis by the examination of 100 twelve-year-old boys would not be justified when the same expenditure for the examination of an equal number of seventeen-year-old girls would reveal three or four cases.

Examinations are sometimes confined to schools situated in poor and congested districts on the assumption that a higher incidence of tuberculosis will be discovered. While it is true that the incidence of asymptomatic tuberculosis is higher in children from districts where the death rate from tuberculosis is high, in most communities each high school receives students from families differing widely in social and economic circumstances. On analysis it may be found that the death rates correspond closely in school districts that appear to differ widely in the economic status of their inhabitants. In Philadelphia we have found an almost uniform incidence of significant tuberculous lesions in children from high schools in all parts of the city.

Age and sex are the only factors which should influence selection within the school of students for examination. Children who are in intimate contact with tuberculosis at home will show a higher incidence of asymptomatic tuberculous lesions, but a reliable history of contact is rarely obtained from high school students. Furthermore, an important feature of the survey method is the detection of tuberculous lesions in persons who have unknowingly been exposed to tuberculosis.

The incidences of infection and of asymptomatic lesions have repeatedly been shown to be equally high in healthy, robust children and those who are delicate or sickly in appearance. Selection for examination on the basis of underweight, pallor, listlessness, or other evidence of frailty, is without value in the detection of asymptomatic tuberculosis. Nor can children who are likely to have asymptomatic lesions be selected by physical examination. Adult type infiltrations, not sufficiently advanced to cause symptoms, are manifested only in very rare instances by physical signs. Restriction of the tuberculin test and X-ray to children with slight or suspected abnormal physical findings will reveal as a rule the same incidence of asymptomatic tuberculous lesions found in apparently normal children. Moreover, definite harm may be done by a physical examination which reveals no abnormality, since it gives a false sense of security to students who have serious asymptomatic disease.

CONSENT TO EXAMINATION

In most programs, the necessity of obtaining consent of parents or guardians seriously limits the number of students examined. In the past this limitation has been particularly marked when the tuberculin test was employed.

The high school pupil has reached the age when he is permitted to decide for himself whether he will be examined and at this age the young man or woman takes good health for granted. Our experience in Philadelphia is probably typical. When the tuberculin test was included in our program the number requesting examination ranged from 28.3 per cent of pupils in a school whose principal and teachers urged the examination to 13.3 per cent in a school whose authorities were antagonistic. When the tuberculin test was omitted, the percentage requesting examination increased from 28.3 to 58.1 per cent in the same school under identical circumstances but in different years. Apparently dislike of the tuberculin test deters many high school pupils from submitting to examination, while approval of teachers is an important influence in persuading others to be examined. Many, however, are indifferent, regardless of the type of examination offered and the influence that is brought to bear upon them. The ease with which consent was obtained in our survey in 1937, when 50 per cent of students accepted the tuberculin test, provided an encouraging contrast to the apathy and resistance encountered in similar surveys ten years ago. However, unless educational efforts succeed beyond present expectations in bringing about universal recognition of the value of tuberculosis case-finding methods, their use must be made compulsory by incorporation in the routine health examination if they are to achieve their full value by general application.

THE TUBERCULIN TEST

Although it gives no specific information regarding the presence of significant tuberculous disease, the tuberculin test forms an important part of tuberculosis case-finding methods. It is an indication of the extent of tuberculous infection in a community and provides a means of determining the need for special effort in certain groups as well as indicating other groups in which case-finding is not likely to be profitable. The efficacy of the tuberculosis control program in a community may be measured by changes in the incidence of tuberculous infection shown by tuberculin testing at intervals or by comparison with the incidence in similar communities where the program is not in effect.

For practical purposes, the tuberculin test selects from the general population those individuals who consciously or unconsciously have been exposed to tuberculosis and in whom further examination may reveal tuberculous lesions. In our experience the number of persons with

significant tuberculous lesions who fail to react to tuberculin is so small as to be negligible.

The technique of tuberculin testing is now fairly well standardized. The intracutaneous or Mantoux test is commonly employed, because an accurately measured quantity of tuberculin can be injected and it is possible to compare the tuberculin sensitivity of different individuals or of the same individual at different times. Although admittedly less accurate, the percutaneous or Pirquet test is still employed in some communities, because it is believed to arouse less opposition in children and adults and is somewhat more easily applied. The same may be said of patch testing, now in the experimental stage.

The introduction of the standardized tuberculin known as Purified Protein Derivative (PPD) has done much to ensure comparable results, and the use of Old Tuberculin of uncertain potency is diminishing. The initial injection of Purified Protein Derivative is 0.000,02 mg. (12). If there is no reaction to this amount at the end of 48 hours, a second injection of 0.005 mg. is given. Using these amounts, the results are practically identical with those obtained with the most potent preparations of Old Tuberculin in the conventional dosages of 0.01 mg. and 1.0 mg.

The advantages of a test employing only one injection are obvious, but no dosage has been found that is entirely satisfactory. A high percentage of persons with asymptomatic tuberculosis will be found among the reactors to 0.000,02 mg. PPD. A somewhat higher percentage will react to a single test employing an intermediate dosage, usually 0.000,5 mg., but with this amount there is danger of producing severe reactions. The importance of obtaining results comparable with studies in other communities as well as with former studies employing Old Tuberculin is a factor in favor of the standard two dose test.

Little training is necessary to read tuberculin reactions with reasonable accuracy. Slightly positive reactions are overlooked sufficiently frequently, however, to make some training in the interpretation of the test desirable.

INCIDENCE OF INFECTION

It is a familiar fact that the incidence of infection as demonstrated by the tuberculin test rises with increasing age. Former studies in Europe and eastern cities of the United States led to the belief that sensitivity to tuberculin was almost universal in adult life. Many investigations during the past decade have shown, however, a wide variation in the

incidence of reactors in different sections of the country. This geographical variation has been emphasized in Whitney and McCaffrey's summary of the extensive studies made by the National Tuberculosis Association (13) as well as in Long and Seibert's report on the incidence of infection in college students (14). College men and women in the East showed the highest percentage of reactors, namely 40 to 60 per cent. Positive reactions were encountered less frequently (30 to 50

TABLE 7

Tuberculin reaction in children of high school age

	YEAR	AGE	NUMBER TESTED	NUMBER POSITIVE	PER CENT POSITIVE
		years			
Philadelphia (1)	1928	12–19	1,249	1,009	80.8
Kingston, Jamaica (15)	1934	10–19	1,091	879	80.5
Blackfeet Indians, Montana (16)	1936*	10–20	618	433	70.1
New York City (7)	1930	13–14	1,000	673	67.3
Philadelphia	1937*	14–20	1,248	807	64.6
Silver City, N. Mex. (17)	1936*	16–20	52	33	63.5
Minneapolis (8)	1926	12–15	665	399	60.0
Negroes of rural South (18)	1933	10–19	4,095	2,385	58.5
Oakland and Alameda, California (19)	1932	12–15	861	413	47.9
Los Angeles (6)	1936*		4,033	1,761	43.7
Massachusetts (20)	1930†	12–15	15,328	5,032	32.8
Detroit (9)	1936†	14–19	9,594	2,380	24.8
Minneapolis (4)	1936	12–15	1,398	311	22.2
Rural Pennsylvania (21)	1936*	10–19	10,358	2,250	21.7
Rural Michigan (22)	1935	10–19	4,202	842	20.0
Cattaraugus County, New York (23)	1933	13–19	705	111	15.8
Rochester, Minn. (24)	1932	11–19	1,328	154	11.6
Rexburg, Idaho (25)	1936*		651	28	4.3

* Tuberculin test was done with intracutaneous injection of PPD.

† Tuberculin test was done with percutaneous administration of OT.

All other tests were done with intracutaneous OT.

per cent) in college students in the Far West, and much less frequently (20 to 30 per cent) in students in the Middle West.

In table 7 in which data on the incidence of infection in children of high school age have been selected from the reports of various authors, a similar geographical variation is shown. Philadelphia and New York report the highest frequency of positive reactors, in contrast to recent figures from Minneapolis. California cities (6, 19) occupy an intermediate position.

In suburban and rural districts the incidence of infection is much lower

than in large cities and is generally higher in the East than in the Middle West. In contrast to the low incidence of infection generally reported in rural communities are the high figures reported among Negroes in the rural South and among Indians in the Northwest as well as among white children of resort and sanatorium areas; such as New Mexico. It is clear that *a priori* assumptions as to the incidence of tuberculous infection in a community should be confirmed by the tuberculin test. In communities or groups in which the incidence of infection is high, use of the skin test to exclude the uninfected from X-ray examination affords no significant saving. Where the infection rate is low, however, failure to employ the tuberculin test results in the needless application of expensive X-ray examination to a large group in whom significant tuberculosis will not be found.

METHODS OF X-RAY EXAMINATION

The most important procedure in tuberculosis case-finding programs is X-ray examination, which affords the most accurate and in many instances the only means of detecting the presence, extent and characteristics of tuberculous lesions in the lungs. X-ray examination in case-finding programs may be applied to all subjects without a preliminary tuberculin test or it may be restricted to those positive to tuberculin. The tuberculin test indicates infection only, and is without value as a case-finding method unless X-ray examination is made. A positive tuberculin reaction has no clinical significance in the individual case without knowledge of the roentgenological findings.

Various methods of X-ray examination, including stereoscopic and single celluloid films, paper films and fluoroscopy, have been widely used in case-finding.

The celluloid film taken with modern apparatus capable of making satisfactory exposures of 0.1 second at a target-film distance of 50 to 60 inches remains the method of choice. Stereoscopic films need not be employed for routine purposes. Recent improvements in fluoroscopic screens and in the technique of paper-film roentgenography have greatly improved the accuracy of these methods, and they are valuable when the equipment necessary for satisfactory celluloid films is not available. Particularly in programs in which preliminary tuberculin testing is not feasible and the entire group must be X-rayed, the usefulness of fluoroscopy and paper films is increased by their lower cost. Weyl, Warren

and O'Neill have recently discussed the relative merits of these methods (26).

VARIATIONS DUE TO METHOD, TECHNIQUE AND INTERPRETATION

Uniformity of application and interpretation of the tuberculin test using Purified Protein Derivative is now possible so that variations in results can be accepted as due to actual differences. This, unfortunately, cannot be said for X-ray studies.

An example of the influence of changes in method is shown in table 8, which gives the incidence of calcified childhood type lesions found in Philadelphia. The apparent decline in the past decade is almost certainly due in large measure to the differences in method used. Similar

TABLE 8

Variations in incidence of calcified primary lesions according to X-ray method

GROUP	YEAR	PERCENTAGE WITH LESIONS	X-RAY METHOD
High School E (Boys)	1927	18.6	Stereoscopic pair and oblique film
High School F (Girls)	1928	22.6	Stereoscopic pair and oblique film
Teachers' training college:			
Students	1931	12.7	Stereoscopic pair
Applicants	1932–34	13.0	Stereoscopic pair
High Schools	1931–34	12.6	Stereoscopic pair
High School E (Boys)	1937	9.7	Flat film
High School F (Girls)	1937	9.3	Flat film

or wider variations must be expected if the results of studies using celluloid films are compared with the results of studies employing paper films or the fluoroscope.

In addition to discrepancies due to use of dissimilar methods, the results differ so widely in similar communities when the same method is used that the differences cannot be accepted as actual but must be attributed in large part to variations in X-ray technique and interpretation. The quality of films, the diagnostic criteria employed, and the training and experience of the roentgenologist are all variables affecting the reported incidence.

Reports on the frequency of childhood type lesions show a wide variation, but even greater differences are reported in the incidence of the

clinically more significant apical infiltrations. This discrepancy is not as important as the figures suggest, because differences in method and interpretation cause dissimilar results chiefly through omission of the slighter and less significant lesions. Although failure to detect minor abnormalities does not detract greatly from the practical results of case-finding, it is misleading to the epidemiologist. It should be recognized, moreover, that more extensive lesions are not infrequently disregarded, particularly by roentgenologists who, accustomed to the gross changes of advanced disease, fail to be impressed by the smaller, asymptomatic lesions which are precisely what is being sought in case-finding programs. Present efforts to standardize and improve technical methods in chest roentgenology must be accompanied, as Weyl, Warren and O'Neill have suggested, by efforts toward more uniform and accurate interpretation.

VARIATIONS DUE TO AGE, SEX AND RACE

The age, sex and race of the children examined also appear to influence the incidence of tuberculosis found in high school surveys. The results of examinations made during the past decade in Philadelphia have been studied in an attempt to determine the importance of these factors.

It has been pointed out that the incidence of clinically significant tuberculous infiltrations is very low before puberty. The number of significant lesions found in preadolescent white children in Philadelphia was so low that examinations in elementary schools were discontinued. We have already mentioned the survey of school boys in a small Pennsylvania city in which no instance of a clinically significant lesion was found on examination of 495 children below the age of 14. In New York, Barnard, Amberson and Loew (7) failed to find a single case of adult-type tuberculosis in 1,000 white school children aged 13 and 14 years.

The rise in frequency of adult-type infiltrations during adolescence is indicated in table 9, which gives the results of examinations of 10,508 high school and normal school students in Philadelphia. The increase with age is evident in both sexes and in white and colored children. The incidence of apical infiltrations in the older age groups is remarkably high (3.4 per cent in boys and 6.8 per cent in girls aged 18 and 19 years), but even higher figures have been reported in adult groups. Pillsbury (27) recently found adult-type disease in 7 per cent of the young men in a Civilian Conservation Corps Camp.

The incidence of adult-type infiltrations in adolescents differs mark-

edly in the two sexes. In our series apical lesions occurred in 77, or 1.8 per cent, of 4,156 boys as compared with 206, or 3.2 per cent, of 6,361 girls. The results in table 9 show this difference in each age group and in both white and colored children. It is apparent that differences in age and sex can be responsible for marked variations in the incidence of asymptomatic tuberculous lesions found in adolescent children in school surveys.

A greater susceptibility of the Negro to tuberculosis is generally accepted, and in several high school surveys a higher incidence of asymptomatic lesions has been reported in colored children. Studies in the elementary schools in Philadelphia showed that clinical tuberculosis in colored children before puberty was not infrequent, in contrast to the

TABLE 9

Incidence by age groups of tuberculous lesions of adult type 1927–1937

AGE	WHITE				NEGRO			
	Male		Female		Male		Female	
	Number examined	Number with lesions	Number examined	Number with lesions	Number examined	Number with lesions	Number examined	Number with lesions
years								
12–13	76	2	55	1	0	0	0	0
14–15	842	7(0.8%)	1,343	24(1.8%)	19	0	69	2
16–17	2,374	40(1.7%)	3,555	102(2.9%)	72	0	314	6(1.9%)
18–19	653	22(3.4%)	739	50(6.8%)	60	1	182	11(6.0%)
20–21	56	5	87	9	4	0	17	1
Total....	4,001	76(1.9%)	5,779	186(3.2%)	155	1(0.6%)	582	20(3.4%)

findings in preadolescent white children. Among the high school and teachers' training school students examined in Philadelphia, there were 737 colored children. Although 21, or 2.9 per cent, were found to have apical tuberculosis compared with 2.7 per cent in white children, a preponderance of females and older students appears to account for the higher incidence in the group of Negroes studied. In fact, the results in table 9 show that in each sex colored children had a somewhat lower incidence of apical lesions than white children of corresponding age.

There appears to be a significant difference, however, in the incidence of serious lesions. The proportions of grade 1, 2 and 3 lesions occurring in 10,508 children are shown in table 10. While the more advanced grade 3 infiltrations constituted approximately a third of the lesions

found in white children, more than half of the lesions found in colored children were sufficiently extensive to be classed in grade 3. Moderately or far advanced tuberculosis constituted 9.5 per cent of the total number of apical lesions found in colored children, while only 6.5 per cent of the lesions in white children were of similar extent. In surveys in which the slighter, less extensive infiltrations are overlooked or disregarded, colored children will appear to have a much higher incidence of adult-type tuberculosis than white children.

TABLE 10

*Incidence by age groups of various grades of tuberculous lesions of adult type 1927–1937**

AGE	MALE				FEMALE			
	Total lesions	Grade 1*	Grade 2	Grade 3	Total lesions	Grade 1	Grade 2	Grade 3
				White				
years								
12–13	2	1	1		1		1	
14–15	7	2	2	3	24	10(42%)	5(21%)	9(37%)
16–17	40	21(53%)	5(13%)	14(34%)	102	53(52%)	17(17%)	32(31%)
18–19	22	12(55%)	3(13%)	7(32%)	50	24(48%)	10(20%)	16(32%)
20–21	5	3	1	1	9	8		1
Total....	76	39(51%)	12(16%)	25(33%)	186	95(51%)	33(18%)	58(31%)
				Negro				
12–13	0				0			
14–15	0				2			2
16–17	0				6	3	0	3
18–19	1			1	11	3(37%)	3(27%)	5(46%)
20–21	0				1			1
Total....	1	0	0	1(100%)	20	6(30%)	3(15%)	11(55%)

* Description of lesions included in grades 1, 2 and 3 is found on page 415.

INCIDENCE OF TUBERCULOUS LESIONS IN ADOLESCENT CHILDREN

The results of representative high school surveys reported by various investigators are shown in table 11. Childhood-type lesions were found in less than one per cent of the students in Massachusetts, where the Pirquet test was used to select children for examination, and in Ulster County, New York, where fluoroscopic examination was employed. In Oakland, California, however, 16.2 per cent of the high school pupils were found to have childhood-type lesions by fluoroscopy, and the in-

TABLE 11

Results of X-ray examination in children of high school age

LOCALITY	YEAR	METHOD	AGE	TOTAL EXAMINED	TUBERCULIN POSITIVE	TOTAL X-RAYED	TUBERCULOUS LESIONS*	
							Childhood type	Adult type
			years					
Philadelphia (1)	1928	3 films	12–20	1,249	1,009	1,005	272 (21.8%)	24 (1.9%)
New York (7)	1930	3 films	13–14	1,000	893	893	184 (18.4%)	
Philadelphia	1931–34	2 films	13–21	6,264		6,264	844 (13.5%)	162 (2.6%)
Philadelphia	1937	1 film	14–20	1,248	807	825	123 (9.9%)	29 (2.3%)
Los Angeles (6)	1935–36	1 film	Grades 10, 11, 12	4,033	1,761	1,625	420 (11.1%)	22 (0.5%)
Rural Pennsylvania (20)	1936	1 film	10–19	10,358	2,250	950	236 (5.8%)	5 (0.1%)
Buncombe Co., North Carolina (28)	1935	1 film	13–20	3,235	522	407	59 (2.3%)	6 (0.2%)
Detroit (9)	1936	1 film	14–19	9,594	2,380		356 (3.7%)	35 (0.4%)
Massachusetts (29)	1935–36	1 film	Grades 7, 9, 11	69,964	14,345	14,963	679 (1.0%)	25 (0.04%)
Oakland, California (18)	1936	Fluoroscopy	Grade 12	4,272		4,272	693 (16.2%)	6 (0.1%)
Ulster Co., New York (30)	1935	Fluoroscopy	Grades 9, 10, 11, 12	1,362	446	410	9 (0.7%)	5 (0.4%)
New Haven (31)	1932	Paper	11–20	5,340		5,340	310 (5.8%)	7 (0.1%)

* Percentages calculated assuming children who completed their examinations were typical samples of group given tuberculin test.

cidence was 3.7 per cent in Detroit, where the same procedure as that employed in Massachusetts was used. The highest incidence of lesions of childhood type was reported in New York (18.4 per cent) and in the 1928 Philadelphia survey (21.2 per cent). In both of these studies, a stereoscopic pair and an oblique film were taken of each reactor to the Mantoux test.

The reported incidence of adult-type infiltrations was also lowest in Massachusetts (0.04 per cent). Using the same procedure of giving celluloid film examination to reactors to the Pirquet test, 0.37 per cent of high school children in Detroit were found to have apical lesions. In surveys in which preliminary tuberculin testing was not used, paper film examination in New Haven discovered 0.14 per cent with adult-type disease, and fluoroscopic examination in Oakland showed 0.13 per cent. A survey in rural Pennsylvania in which reactors to the intracutaneous test using PPD were given X-ray examination with low-power apparatus revealed an incidence of apical infiltrations of 0.11 per cent. Examination of 1,000 students in New York City, employing the Mantoux test and stereoscopic films and confined to children aged 13 and 14 years, showed no instance of an adult-type lesion. Studies in Philadelphia using celluloid films with or without preliminary tuberculin testing have shown repeatedly an incidence of adult-type disease of about 2 per cent, fifty times that reported in Massachusetts school children.

Explanation of the wide variations in results indicated above requires consideration of all the factors that may have affected the incidence of asymptomatic tuberculosis reported. A number of these factors influence the actual incidence of lesions, others cause differences through the failure, in varying degree, to demonstrate or recognize lesions actually present. It is reasonable to expect that the incidence should be high in the East, slightly lower in the Far West, and much lower in the Middle West, for tuberculin testing and death rates indicate corresponding differences in the opportunity for infection. The frequency of lesions should, for the same reason, be lower in rural and suburban districts than in metropolitan centres. It is clear, also, that surveys of groups containing older children and a preponderance of females should reveal a higher incidence of tuberculosis than surveys of young children with a preponderance of males.

The accuracy of the results reported is determined by the choice of method, the diagnostic criteria adopted, and the training and experience of the roentgenologist. Thus, examination of reactors to the Mantoux

test will include practically all of the students who have tuberculous lesions, while if the Pirquet test or a single intracutaneous test is used a considerable number of children with lesions may fail to receive X-ray examination. The difficulty of distinguishing with certainty small apical infiltrations by the fluoroscope, paper films or celluloid films taken with low-power apparatus results in reports of a low incidence of tuberculosis in surveys employing these methods. Even in studies having the advantage of satisfactory celluloid films, differences in diagnostic standards produce widely varying results depending upon whether all apical infiltrations are reported or only those sufficiently extensive to be deemed of immediate clinical importance. Roentgenologists without special training and experience in the detection and interpretation of asymptomatic tuberculous infiltrations will as a rule disregard the small lesions which are not considered significant in clinical practice.

In view of these considerations, it is impossible to express an opinion on the actual frequency with which adult-type tuberculosis occurs in high school children. Accurate results can be obtained from surveys in which investigators with special experience give X-ray examination with modern technique and celluloid films to all reactors to the standard intracutaneous tuberculin test, but the incidence will vary widely depending upon the age and sex of the children examined and on the size and geographical location of the community.

SIGNIFICANCE OF ASYMPTOMATIC TUBERCULOSIS

The significance of tuberculous lesions found in adolescent children can be established only by observation of a large group over a period of years. It should be recognized that it is desirable to determine the prognosis both in persons who accept treatment and in those who fail to follow the regimen advised. No studies of this nature embracing adequate numbers of students have been reported, and conclusive evidence is lacking as to what proportion of the tuberculous infiltrations found in apparently healthy adolescent children may be expected to progress to clinical disease, and what proportion may retrogress without causing illness. These proportions will vary with the character and extent of the lesions, the treatment taken, and presumably with the presence or absence of intimate contact.

It is particularly difficult to induce adolescent children to remain under observation, for at this age good health is taken for granted. Moreover, following graduation from high school, many naturally prefer

the care of private physicians or more conveniently located clinics and hospitals, so that it is almost impossible for any one institution in a large city to keep a significant proportion under observation. In the young men and women who return for periodic examinations, it is extremely difficult to determine the extent to which they have carried out the treatment or prophylactic measures recommended.

Our reëxamination in 1933 (32) of the group which had been examined in 1927–1928 indicated that children with calcification of the tracheobronchial lymph nodes are not more likely than others to develop apical tuberculosis later. Reëxamination of a small group in whom apical infiltrations had been found suggested that latent lesions of slight extent do not progress under an altered regimen, while more extensive lesions with or without symptoms or physical signs often cause serious disease in the absence of adequate treatment.

The group of high school children examined between 1931 and 1934 was invited with the coöperation of their family physicians to return for periodic X-ray examination. While sixty per cent returned for at least one examination, only twelve per cent remained under our observation for more than two years. This could be construed as an indication of the futility of the survey method of case-finding as a measure for tuberculosis control. However, merely to warn an adolescent of the presence of a tuberculous lesion may be of benefit, since, should progression to the stage of clinical manifestations occur, previous knowledge of a latent lesion will result in an early diagnosis. Moreover, knowledge that a tuberculous lesion is present exerts a restraining influence to some degree on the most heedless person, and even trivial modification of regimen may suffice to prevent the progression of lesions of slight extent.

In spite of these considerations, the seriousness of asymptomatic apical tuberculosis is shown in a limited group in which a satisfactory follow-up has been obtained. Twenty-three of the twenty-nine students of the municipal teachers' training college who were found in 1931 to have apical lesions (table 12) have been observed over a period of from three to six years. Of eleven white students with grade 2 and grade 3 lesions, two died, three developed clinical disease, four did not progress to the stage of clinical disease and two did not remain under observation; of five colored girls with similar lesions, three died, one developed clinical tuberculosis requiring sanatorium care, and one remained under observation only two years. The prognosis in Negroes must obviously be considered much more serious.

TREATMENT

The majority of patients with advanced tuberculosis die from their disease. Often, when symptoms make their first appearance, the lesion is already in an advanced stage. Treatment, if it is to be applied most successfully, should be instituted before symptoms develop.

When an adolescent or young adult is found to have an apical infiltration suitable measures for the control of the lesion should be instituted (33). For lesions that consist of slight apical pleural thickening with strands or sharply defined spots in the lung immediately below the apex (grade 1), no alteration in regimen is indicated unless extension of the lesion is noted. Observation by X-ray is advisable at intervals of four months to one year depending upon the presence of intimate contact. In a second group (grade 2), in which the lesion is small but not strand-

TABLE 12

Tuberculous lesions of adult type in students of teachers' training college, 1931; results of subsequent observation

TYPE OF LESION	NUMBER WITH LESIONS	NO CLINICAL DISEASE (LESS THAN 3 YEARS)	NO CLINICAL DISEASE (3 TO 6 YEARS)	CLINICAL DISEASE	DEATHS FROM TUBERCULOSIS
Grade 1*	13	3	10		
Grade 2*	7	2	3	2	1
Grade 3*	9	1	1	7	4
Total	29	6	14	9	5

* Description of lesions included in grades 1, 2 and 3 is found on page 415.

like in the film, an altered regimen which includes extra rest, additional nourishment, avoidance of fatigue, and better care of personal hygiene, may be instituted. X-ray examination is desirable at three-month intervals to make certain that the lesion is not extending. A similar regimen is advisable for more extensive lesions (grade 3) that are strandlike in appearance, but if symptoms or physical signs are present, or if the lesion appears acute and progressive in character, sanatorium care or its equivalent should be recommended.

Unfortunately the value of the early discovery of tuberculosis is lessened not infrequently when the parents and child consult the family physician and are assured after questioning and physical examination that the child is perfectly healthy. Further education is necessary to convince the medical profession that progressive, potentially dangerous

tuberculosis can be present without causing even slight symptoms or physical signs. The frequency with which tuberculosis progressed to a fatal termination in the 29 students of the teachers' training college who were found to have apical infiltrations illustrates the serious consequences of reluctance to institute intensive therapy when the patient's health has not been demonstrably impaired.

The tuberculosis control program in the high school cannot be considered adequate unless provision is made for supervision and treatment of the cases discovered; this is important for students with less extensive lesions as well as for those with more advanced disease who are excluded from school. Replies to a questionnaire sent to school and health authorities of large American cities indicate a serious deficiency in this regard. In only seven instances was special attention said to be given to students with asymptomatic lesions. Restriction of activities, including exclusion from athletics, provision of special lunches, advice regarding extracurricular conduct, and reference to private physician or dispensary for supervision were among the measures employed, and most programs included only one or two of these measures.

It is clear that students with positive sputum or with lesions suggesting that tubercle bacilli may appear in the sputum should be excluded from school to prevent infection of others. Because school attendance may be detrimental to health, sanatorium care is advisable also for students with slight or no symptoms who have acutely progressive infiltrations. Students with less threatening lesions should be placed under a suitable regimen, including altered curricular requirements and exclusion from athletics. School or community nurses should be employed to supervise the extramural activities of these students in order to obtain proper rest, adequate nourishment and suitable hygienic habits.

PLACE OF THE HIGH SCHOOL PROGRAM IN THE COMMUNITY CAMPAIGN

While it is desirable that measures for the control of tuberculosis in high school students be under the direction of the official medical authorities of the school system so that the aim of universal application may be realized, the program should be carried on in coöperation with agencies conducting the community campaign against tuberculosis. High school students, in whom significant tuberculous lesions are not infrequent, form a large group. In the United States in 1936 there were approximately ten million persons of high school age, and more than six million were in attendance in public high schools (34).

The relative value in the community tuberculosis control program of examination of the numerically large group attending high school will depend upon the proportion of all clinical tuberculosis that can be detected in an asymptomatic or early clinical stage in adolescent children, if it is assumed that the incidence of lesions is the same in those who attend high school and those who do not.

In attempting to determine the difference in the incidence of tuberculosis between the group attending high school and the group of similar age who are not at school, a number of factors might be considered. However, discussion of social and economic influences, the possibility of contagion in classrooms, the dangers of certain hazardous occupations, and the hygienic habits of student and worker leads to no definite conclusions. The question can be solved only by comparable studies on the incidence of tuberculosis in school and industrial groups of the same age. This has not yet been done. Some insight into the influence of these factors might be obtained by a comparison of the frequency of tuberculous lesions in high school and college students. If the frequency is not greater than in high school students, as would be expected with increase in age, we may fairly conclude that economic and social factors are operative in lessening the frequency of tuberculosis. Unfortunately, college surveys do not give a consistent answer. Studies at Vassar (35) and Smith (36), and at Yale (37), indicate an incidence much lower than that found in most high school surveys. Nicholson (38) found that young women dying of tuberculosis in New York and Detroit exceeded the average educational level of the population of those cities, and that the proportion who had attended college closely approached that of the population as a whole. Examinations at the University of Wisconsin (39) and the limited study made by the Henry Phipps Institute in a group of undergraduates at the University of Pennsylvania in 1930 revealed an incidence considerably higher than that encountered in the average high school survey. Thus it is clear that the belief that there is less tuberculosis in adolescents at school than in their contemporaries in industry, is not satisfactorily proved.

In Philadelphia in 1937 there were 1,165 deaths from pulmonary tuberculosis in persons over 15 years of age. Two hundred and one of the 441 deaths in women and 152 of the 724 deaths in men occurred between the ages of fifteen and thirty years. The high incidence of tuberculous infiltrations found in older high school students, particularly in girls, suggests that a large part of the tuberculosis resulting fatally be-

tween 15 and 30 years of age is present in an asymptomatic stage in adolescence. Nicholson's study of young women dying of tuberculosis in New York City showed that 21 per cent had their initial symptoms while attending school, and another 12 per cent had been out of school less than a year when symptoms appeared. Presumably a much larger number had asymptomatic lesions during school years which would have been revealed by X-ray examination. Recently skepticism has been expressed as to the wisdom of examining high school children, since a higher incidence of lesions may be found in adult groups (40). It should be recognized, however, that while all the adult-type infiltrations discovered in adolescent children can be presumed to be relatively recent and hence clinically important, many of the apical lesions found in adults are old and obsolete. Moreover, if case-finding methods are restricted to older groups, examination will not be given to the very considerable number who develop clinical tuberculosis at an earlier age.

It may be concluded that the universal application of X-ray examination to older high school students would be an important measure in the community campaign against tuberculosis, and an economically sound expenditure of public funds.

SUMMARY

1. Examinations employing standard methods of tuberculosis case-finding were first given to high school students in Philadelphia in 1927–1928. In order to determine any change in the incidence of infection during the past decade a survey was made in 1937 of the two schools in which the program was originally instituted. Results of this survey as well as results of examinations made in other schools from 1931 to 1934 are reported.

2. The percentage of high school students reacting to tuberculin declined from 80.8 per cent in 1927–1928 to 64.6 per cent in 1937. In girls the incidence of infection declined from 89.9 per cent to 61.9 per cent and in boys from 74.1 per cent to 68.0 per cent. The incidence of infection in Jewish, Italian and other white students was less at each age in 1937 than in 1927–1928. There was no decline in the incidence of infection among Negroes.

3. X-ray examination given to reactors to tuberculin revealed adult-type tuberculous infiltrations in 2.7 per cent of the girls tested in 1927–1928 and in 2.9 per cent of the girls tested in 1937. In boys the inci-

dence was 1.4 per cent in 1927–1928 and 1.6 per cent in 1937. Between 1931 and 1934 X-ray examination given to 6,264 students from various high schools without preliminary skin testing showed adult-type infiltrations in 3.1 per cent of girls and 1.9 per cent of boys. Examination of younger girls attending a vocational school revealed adult-type lesions in 1.2 per cent, whereas examination of older students in a teachers' training college demonstrated similar lesions in more than 5 per cent. The combined results of the examinations made in 1927–1928, in 1931–1934, and in 1937 showed that the incidence of adult-type lesions varied from 0.8 per cent in boys and 1.8 per cent in girls aged 14 to 15 years, to 3.4 per cent in boys and 6.8 per cent in girls aged 18 to 19 years.

4. For purposes of more accurate comparison the adult-type lesions were divided into three grades according to their extent and appearance in the X-ray film. In each survey, approximately one-half of the lesions found were small, strandlike supraclavicular infiltrations of doubtful clinical significance (grade 1). The remaining lesions were either flocculent infiltrations limited to the lung above the clavicle (grade 2) or more advanced infiltrations appearing below the clavicle (grade 3). In 1937, as in 1927–1928 and in 1931–1934, the proportion of lesions included in grade 3 closely approximated 33 per cent.

5. The tuberculin test is a valuable preliminary to X-ray examination in case-finding programs. Surveys indicate that the percentages of adolescent children who react to tuberculin vary widely in the United States. The incidence of infection is higher in cities than in suburban and rural districts, is highest in the East and lowest in the Midwest. Use of the tuberculin test as a screen is particularly valuable in communities where the rate of infection is low.

6. In Philadelphia during the past decade the incidence of infection in adolescent children failed to decline as sharply as the mortality from tuberculosis, but the decrease in both indicates that the opportunity for contact with tuberculosis is considerably less than ten years ago. However, the decline in both incidence of infection and death rate from tuberculosis has been less marked than that reported from Rochester, New York, Minneapolis and Detroit, and the percentage of high school students in Philadelphia who react to tuberculin remains considerably higher than the percentages recently reported from other American cities.

7. The percentage of reactors in adolescent children in the present

study is only slightly higher than the percentage of reactors in young elementary school pupils a decade ago. Since many of the younger children presumably acquired a positive reaction during the interval an almost equal number must have lost their sensitivity to the dosages of tuberculin employed.

8. The results of X-ray examination recently reported differ widely not only because of actual variations in incidence depending upon the age and sex of the children and the size and geographical location of the community, but also through failure in varying degree to demonstrate or recognize lesions actually present. Although definitely useful under certain circumstances, fluoroscopy, paper films and celluloid films taken with low-power apparatus do not give results comparable with those obtained with celluloid films and modern technique. Additional difficulty in the comparison of results arises from discrepancies in interpretation due to variations in diagnostic standards and experience.

9. X-ray examination of high school students in Philadelphia shows no significant change between 1927–1928 and 1937 in frequency or severity of adult-type lesions. Although the incidence is considerably higher than that reported in other American cities, studies in other high schools in Philadelphia indicate that the results are not due to selection of children from congested districts. The incidence of apical lesions is low in young children and increases progressively during adolescence. The frequency in adolescents is greater by almost fifty per cent in females than in males of the same age. The total incidence is approximately equal in white and colored children, but extensive and serious lesions are more prevalent among Negroes.

10. The prognosis and significance of asymptomatic lesions is difficult to establish, particularly in high school children. Study of a limited group indicates that the lesser infiltrations are easily controlled, but that the more extensive infiltrations, particularly in Negroes, are of serious clinical significance. Treatment must depend on the roentgenological extent and character of the lesions, and supervision should be provided within the school system and at home for students with disease not sufficiently threatening to justify exclusion from classes.

11. Examination of older high school students, particularly of girls, will discover a considerable proportion of the tuberculosis that is disabling or fatal in early adult life. Application of the survey method of case-finding in high schools can be an effective factor in the control program of the community.

Acknowledgment is due Dr. Walter S. Cornell and Dr. J. Hart Toland of the Division of Medical Inspection in the Philadelphia public schools for their unfailing coöperation.

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TUBERCULOSIS STUDIES IN TENNESSEE[1]

Roentgenological Evidence of Tuberculous Infection in Relation to Tuberculin Sensitivity in School Children

R. S. GASS, R. L. GAULD, E. F. HARRISON, H. C. STEWART AND W. C. WILLIAMS

The Tennessee Department of Public Health has devoted special attention to studies of tuberculosis since 1928. A remarkable tendency toward the deposition of calcium in lung fields or tracheobronchial lymph nodes has been noted, and it seems apparent that calcified lesions as demonstrated by the X-ray are present in a greater proportion of individuals than has been reported in other parts of the country.

The Williamson County study has shown that these calcified lesions were demonstrable in a considerable proportion of individuals with a negative tuberculin reaction. Previous school surveys here and elsewhere have limited almost entirely the making of chest radiographs to children with a positive tuberculin reaction. Previously, little or no attempt was made to determine what proportion of nonallergic children show calcium deposits on X-ray examination. The present survey was undertaken to determine to what extent this occurred, and, if possible, its significance in the epidemiology of tuberculosis.

PROCEDURE

The children in attendance at certain schools in Williamson County, Tennessee, form the basis of investigation in the present study. Nine white and three Negro schools were selected because they were provided with electric current and made possible the use of a portable X-ray machine in the school building. All schools in the county having suitable current were included in the survey and no other selection was made beyond the willingness of the children to coöperate. Very nearly all children in attendance at the time of the survey were included, the total, 6 to 19 years of age, having tuberculin tests and chest radiographs numbering 1,015 white and 276 colored children. The children were

[1] From the Tennessee Department of Public Health. This investigation was made possible by the financial support of the International Health Division of the Rockefeller Foundation.

X-rayed at approximately the same time the tuberculin tests were given (in only 16 instances was there an interval of more than ten days) without reference to the result of the test. If the first film was unsatisfactory, a second was made as soon as possible. The survey was made during the months of January to March, 1937.

Koch's Old Tuberculin was used in the testing. The dilutions in normal saline solution were made as used each day. The tuberculin was of a lot standardized to conform to the requirements of the Henry Phipps Institute, Philadelphia. In giving the test the intracutaneous method of Mantoux was used in doses of 0.01 and 1.0 mg. as described by Aronson (1), 1931, and readings were made 48 hours following administration. At the conclusion of the survey the tuberculin was checked for potency at the Henry Phipps Institute, against Purified Protein Derivative. The results of the check were as follows:

	First Test	Second Test
Number	50	30
Positive PPD	20	15
Positive OT	20	17

This shows that of 50 individuals 20 reacted to the first dose of both PPD and OT, and that of the 30 negative to the first dose, 15 reacted to the second dose of PPD and 17 reacted to the dosage of 1.0 mg. of OT. After the completion of the check, Dr. E. R. Long, Director of the Institute, stated, "I would say that the results secured with your Old Tuberculin and the results with PPD in any large survey would not be significantly different."

As the radiographs were made the individual's tuberculin test card was numbered to correspond to the number exposed on the film. By the use of this procedure, the clinicians were able to read the films by number without knowledge of the results of the tuberculin tests or even the names of the individuals of whom the radiographs were made. At the same time it was a simple matter to relate the X-ray findings to the results of the tuberculin test.

All the films were read by two clinicians (R. S. G. and E. F. H.) quite independently and without knowledge of either the results of the tuberculin test or the other clinician's reading. The two independent readings were then compared. In those cases in which a difference of opinion had occurred the films in question were abstracted from the larger group. Knowing that there had been a difference of opinion, but without knowl-

edge of either the presence of allergy or their own previous readings, the two clinicians then jointly read these films.

An attempt was made to classify the films according to the definiteness and degree of calcification noted. The following classification was used:

0: Negative
- (a) The films called negative by both clinicians on first reading
- (b) The films on which there was disagreement on first reading but which were called negative on joint reading

1: Doubtful
- (a) The films on which there was disagreement on first reading but which were called positive on joint reading
- (b) The films called positive by both clinicians on first reading, on which, in a final review, it appeared that the lesion was not definite enough to be beyond question when viewed by an independent reader

2: Definite calcified lesions, limited in extent

3: Extensive calcified lesions

RESULTS OF TUBERCULIN TESTING

All tests were given and read by the same person. The recorded results were checked by a second person and are given in table 1.

The proportion of reactors is somewhat higher in the colored than in the white children. The proportion of children reacting to the smaller dose of tuberculin is about twice as high in the colored as in the white children.

A slightly different tendency is noted in the two groups with increasing age. The trend is toward an increase in the proportion of reactors with increasing age in the colored children, while in the white children there appears to be no appreciable increase in the proportion of reactors after 10 or 12 years of age. At no single year of age did the percentage of reactors exceed 55 in the white children.

X-RAY FINDINGS IN RELATION TO RESULTS OF TUBERCULIN TESTS

Children with calcified lesions noted on X-ray examination were classified according to the result of tuberculin tests. The percentage frequencies of various X-ray findings were prepared and are contained in table 2.

The proportion of white children with definite calcified lesions is practically the same in the tuberculin-positive as in the tuberculin-negative

group and this proportion is about the same in the tuberculin-positive colored children. In each of these three groups, about one-half the children were noted to have definite calcified lesions. In the fourth group,

TABLE 1

Tuberculin reactions in white and colored school children by single years of age

AGE	WHITE				COLORED			
	Number tested	Tuberculin-positive		Per cent positive 1.0 mg. or less	Number tested	Tuberculin-positive		Per cent positive 1.0 mg. or less
		0.01 mg.	1.0 mg.			0.01 mg.	1.0 mg.	
6	71	1	20	30	17	3	7	59
7	85	5	26	36	15	1	1	13
8	82	2	25	33	13	1	8	69
9	100	6	36	42	24	4	6	42
10	87	12	34	53	32	5	6	34
11	94	3	38	44	24	3	7	42
12	93	5	36	44	37	8	10	49
13	84	8	37	54	31	4	13	55
14	72	10	26	50	26	9	8	65
15	77	9	28	48	18	3	10	72
16	71	5	29	48	9	2	3	56
17	53	7	22	55	12	2	4	50
18	29	6	9	52	12	3	7	83
19	17	5	2	41	6	0	5	83
Total.....	1,015	84	368	44.5	276	48	95	51.8

TABLE 2

Percentage frequencies of various X-ray findings in white and colored children, by result of tuberculin test

X-RAY FINDINGS	WHITE		COLORED	
	Tuberculin-positive	Tuberculin-negative	Tuberculin-positive	Tuberculin-negative
Negative.....	33.2	38.2	38.4	51.1
Doubtful.....	15.7	13.7	12.6	14.3
Definite calcified lesions.....	51.1	48.1	49.0	34.6
Limited.....	35.0	33.2	28.0	20.3
Extensive.....	16.1	14.9	21.0	14.3

the tuberculin-negative colored children, this proportion is somewhat lower, slightly more than one-third. If attention is given to that group with extensive calcified lesions in which there would seem to be much less likelihood of variation in the interpretation of films by various

readers, there is but little variation in the two groups of white children, and only a small variation in the two groups of colored children.

The number of colored children included in the survey group is not sufficiently large to warrant further subdivision and analysis.

Further subdivision of the tuberculin reactors was made for the group of white children. At the time the tuberculin tests were read the degree or extent of reaction was also noted. An area of oedema surrounding the injection site of as much as 5 but less than 10 mm. in greatest diameter was graded as a one-plus reaction. Oedema measuring 10 or more but less than 15 mm. in greatest diameter was classed as a two-plus reaction. Oedema of 15 or more mm. in greatest diameter was regarded

TABLE 3

Percentage frequencies of various X-ray findings in white tuberculin reactors, by extent of reaction

X-RAY FINDINGS	REACTION TO 0.01 MG. OT		TWO-PLUS OR MORE REACTION TO 1.0 MG. OT		ONE-PLUS REACTION TO 1.0 MG. OT	
	Number	Per cent	Number	Per cent	Number	Per cent
Negative	24	28.6	21	28.0	105	35.8
Doubtful	9	10.7	13	17.3	49	16.7
Definite calcified lesions	51	60.7	41	54.6	139	47.4
Limited	32	38.1	28	37.3	98	33.4
Extensive	19	22.6	13	17.3	41	14.0
Total	84		75		293	

as a three-plus reaction. Any reaction, regardless of size, if resulting in necrosis, was classed as a four-plus reaction.

The total number of white tuberculin reactors (452) was divided into three groups, as follows: (*1*) reactions to 0.01 mg. of OT, (*2*) reactions classed as two-plus or greater to 1.0 mg. of OT, and (*3*) reactions one-plus to 1.0 mg. of OT. There appeared to be no significant variations by age in these groups. The results of X-ray examination of these three groups are given in table 3.

A higher proportion of those reacting to 0.01 mg. of OT show calcified lesions than do those with a one-plus reaction to 1.0 mg., while those with a reaction of two-plus or greater to 1.0 mg. occupy an intermediate position. This same difference is observed when the comparison is limited to those with extensive calcified lesions. No difference is noted in the proportion with calcified lesions among those with a one-plus re-

action to 1.0 mg. when comparison is made with the tuberculin-negative white children.

INTERPRETATION OF FILMS BY OTHER OBSERVERS

As the analysis of the material brought out certain points on which there was not agreement with the generally accepted views of tuberculin allergy in relation to evidence of tuberculous infection as shown by X-ray examination, an attempt was made to obtain confirmation of certain observations. A group of 154 films of white children, comprising all films from two schools and a consecutive series from a third school, was collected for further study. The only selection was in an effort to include films which were of better quality. These films were sent to the

TABLE 4

Number of observers noting presence of definite tuberculous lesions, by result of tuberculin test

NUMBER OF OBSERVERS NOTING PRESENCE OF DEFINITE TUBERCULOUS LESIONS	TUBERCULIN-POSITIVE		TUBERCULIN-NEGATIVE	
	Number	Per cent	Number	Per cent
5	20	32.8	23	24.7
4	4	6.6	20	21.5
3	7	11.5	7	7.5
2	6	9.8	4	4.3
1	7	11.5	12	12.9
0	17	27.9	27	29.0
	61		93	

following observers: Dr. E. R. Long, Henry Phipps Institute, Philadelphia; Dr. A. S. Pope, Division of Tuberculosis, Massachusetts Department of Public Health, Boston; Dr. J. H. Korns, Bureau of Tuberculosis, Cattaraugus County, Department of Health, Olean, New York; and Dr. Miriam Brailey, Harriet Lane Tuberculosis Clinic, Johns Hopkins Hospital, Baltimore.

These observers were requested to read the films with particular reference to the presence or absence of evidence indicating tuberculous infection, and in such a way as to allow the classification of the interpretations in three groups, (*1*) those in which evidence of tuberculous infection was definitely present, (*2*) those in which such evidence was definitely absent, and (*3*) those which the reader did not feel able to place in either of the other two groups. At the time the films were read these observers

had no knowledge of the results of the tuberculin tests. After the film readings had been received, groupings were made and summaries returned to the observers. In each instance the reader stated that the interpretation given his readings was a fair one.

As might be expected, there was a good deal of variation in the readings of some of the films, but as the chief point of interest seemed to be the evidence of definite tuberculous lesions, particular attention was given to those films noted as *positive* for such evidence. A division of the data was made according to the result of the tuberculin reactions. The number of positive readings for each individual film was also noted. The results are shown in table 4.

There was complete agreement on the part of the five observations as to the presence of definite tuberculous lesions in 32.8 per cent of the tuberculin-positive reactors and in 24.7 per cent of the tuberculin-negative reactors. Such lesions were noted on at least four of the five observations in 39.4 per cent of the tuberculin-positive children and 46.2 per cent of the tuberculin-negative reactors. This would appear to confirm the observations on the part of the clinicians in this area that evidence of tuberculous infection is present in a considerable proportion of children who do not have a positive tuberculin test. If this is true, the level of tuberculous infection in Williamson County must be appreciably higher than would be shown by the use of the tuberculin test alone as an index of such infection.

Further investigation relating to this subject is being made.

Acknowledgments are made to Drs. Long, Pope, Korns, and Brailey who so generously made interpretations of films for purpose of comparison, to Dr. Long for the check of the tuberculin, and to Dr. W. H. Frost of the Johns Hopkins School of Hygiene and Public Health for suggestions concerning the classification used.

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MASS CASE-FINDING[1,2]

ARTHUR B. ROBINS

The tuberculosis control program of the Bureau of Tuberculosis of the Department of Health can be divided into two broad categories, case-finding and case-supervision. Of the two, case-finding occupies most of our time and effort. There are several reasons for this. Case-supervision in its active phase, that is, treatment, is entirely an institutional problem. Once a case requiring such care, whether it be bed-rest or collapse therapy, is referred to the proper agency our responsibility ceases. It is only resumed when the patient returns from the hospital or sanatorium, and again needs periodic clinic observation. Since the majority of cases are still first discovered in the advanced stage of their disease, the number that recover sufficiently to return to the clinic is significantly less than the total number of cases of tuberculosis found. Also hospital clinics and private physicians supervise a larger proportion of the cases of tuberculosis than they find. As a result, in 1936, 30 per cent of all the new cases of tuberculosis in New York City were first reported by Department of Health Clinics, whereas only 14 per cent of the cases were under our supervision. Lastly, patients discharged for the continuation of pneumothorax therapy are considered to belong in the province of the hospital clinic, rather than the Department of Health. Since pneumothorax is constantly being more widely employed, a greater proportion of cases which otherwise would be returned to our supervision is instead being referred to clinics associated with institutions. This tends to increase further the disproportion between our case-finding and case-supervision activities.

A constant balance between case-finding and case-supervision is necessary however. While it is true that cases must be found to be supervised, the discovery of a case of tuberculosis for which no provision for further care can be made adds little to the control of the disease. The entire

[1] From the Bureau of Tuberculosis, Department of Health, New York City.

[2] Presented at a Clinical Session on Chronic Pulmonary Diseases, under the auspices of the Tuberculosis Sanatorium Conference of Metropolitan New York, Cornell University Medical College, April 13, 1938.

policy of the Department is predicated on the assumption of the need for this balance.

Let us briefly examine the situation as it applies to New York City. There were approximately 5,000 deaths from tuberculosis in this city last year, and close to 9,000 new cases of the disease were found. About 5,000 beds were available for the treatment of tuberculosis at the time. On the basis of the Framingham formula of 9 active cases to each annual death there were 45,000 active cases among the populace. Nineteen thousand of these cases were registered in the central record file of this Bureau, and hence were known. Were we to embark on a case-finding program designed to discover the 26,000 unknown cases, we would be faced with the dilemma of having 15,000 to 20,000 names to add to a waiting list of 250 people for 5,000 beds already constantly occupied. When one adds that such a program would entail the X-ray study of almost the entire population of this city, with its prohibitive cost, the limitations upon case-finding become obvious.

What then is the case-finding program of the Bureau of Tuberculosis? In brief it is the search for tuberculosis in the groups or areas where it is most apt to be found, at the time when it is most likely to be discovered in its incipiency. This should be done at the lowest cost per case found, and as widely as the facilities available for the care of the cases warrant. In addition our activities should be of educational value to the groups examined and the public at large. Several problems are inherent in such a policy. These are, where shall we look, when shall we look, and how shall we look for tuberculosis. I think it fair to state that we do not have the answers to these questions at present. Much of our recent effort has been devoted to analysis of case-finding methods, largely through the medium of sampling studies. Only through the use of such trial and error procedures can we hope to arrive at a sound case-finding program.

From a chronological point of view the starting place for our activities must be the child. Children naturally fall into two groups, the separation occurring at adolescence. Puberty is not only a physiological dividing line, but also a time when the reaction to disease, and in particular tuberculosis, undergoes profound alterations. Our statistical service gives us a clear insight into this difference. In 1937 only 400 cases of tuberculosis were reported in children under the age of 15 in New York City, whereas over 600 cases were discovered in those between 15 and 19 years of age during the same period. Most of the cases in the younger

group were primary infections, only 71 children with reinfection tuberculosis being carried in all the Department of Health Clinics. With these facts in mind we have made little attempt to survey the preadolescent child widely.

For the past six years in coöperation with the East Harlem Nursing and Health Association we have been examining preadolescent children in the East Harlem District of Manhattan. This is an unselected group, 1 to 8 years of age, largely of Italian parentage and of low economic level. Almost 6,000 have been given Mantoux tests, and the positive reactors were X-rayed. Fifty-four cases of childhood type tuberculosis have been discovered but only one case of reinfection tuberculosis has been found. This was detected on serial follow-up and not on the original examination. A somewhat similar study done (conjointly by the Department of Health, the Milbank Memorial Fund and the Mulberry Health Center (1)) during 1935 and 1936 in the Mulberry Health Center district was even less productive. Almost 2,000 elementary school pupils were investigated by tuberculin tests and X-ray. Not one case of reinfection tuberculosis was found. A third survey, carried out in two Catholic protectorates in Richmond at about the same time (2) revealed one case of chronic pulmonary tuberculosis among over 1,500 white children, 3 to 16 years of age. This case occurred in a girl 13 years of age.

From these experiences it is our conclusion that the preadolescent child is not a fertile field for case-finding. The cost is high, the results meagre. If such studies are to be made, tuberculin screening and X-ray examination of the positive reactors are the logical methods of procedure. The educational value of surveys in this group is questionable. The child is too young to profit from his experience, and it is doubtful if the parent is clearly aware of the purpose of the tests, as so many similar injections are given to children at this age. Tuberculin testing of school children has been advocated as a method of finding cases in the families of positive reactors. Our experiences do not confirm this. In the Mulberry district survey the families of positive reactors were studied intensively; 223 individuals in 78 such families were examined by the end of 1936. Only one active case of reinfection tuberculosis was discovered. In fact in more than one-third of the families in which known cases of tuberculosis were present, the grade school children in the family failed to react to the tuberculin test. The present policy of this Bureau is to examine those children in contact with open cases of tuberculosis, and

those presenting pulmonary symptoms, as part of our routine clinic program, but to make no attempt at more extensive surveys of the pre-adolescent group.

The adolescent presents more of a challenge. All mortality and morbidity tables show a sharp rise in the incidence of tuberculosis in the teen ages, particularly in girls. Our own statistics show a fourfold increase in the number of cases in the five year period after 15 compared with the previous five year period. The necessity for a critical analysis of the problem in this group has led us to undertake three surveys in the high schools of New York City during the past year.

Over 6,300 students have been studied in all. The first survey was carried out in Wadleigh High School, a girls' school in Harlem, with a predominantly Negro enrollment; 1,635 girls were X-rayed, approxi-

TABLE 1

Results of surveys in younger children 1935–1936

	AGE	NUMBER OF CHILDREN STUDIED	NUMBER OF CHILDREN X-RAYED	NUMBER OF CHILDREN WITH REINFECTION TUBERCULOSIS
East Harlem Nursing and Health	1–8	5,713	310	1
Mulberry Health Center District	5–16	1,940	326	0
Richmond Protectorates	3–16	1,545	322	1
Total		9,198	963	2

Bureau of Tuberculosis, Department of Health, New York City.

mately 40 per cent of the entire school population; 14 cases of tuberculosis were discovered, 13 in Negro girls and one in a white girl. Three cases were moderately advanced, one far advanced, and the remainder minimal in extent. One had a positive sputum. Three of the girls were 16 years old, seven 17 years old, and three 18 years of age. The age of one was not reported. Most of these girls are in institutions, and one has since died. The incidence of disease in the group X-rayed was 0.9 per cent. We are not satisfied with these results however. Only 40 per cent of the entire school were examined, and we suspect that those most in need of examination may not have been included, thus failing to give us a true picture of the amount of disease present in this group.

At about the same time the opportunity for a more complete study presented itself. The Benjamin Franklin High School, a boys' school in East Harlem, predominantly Italian in its enrollment, offered its facil-

ities. The authorities of the school assured us that we could examine almost the entire school body, using both tuberculin test and X-ray. After an intensive educational campaign we secured requests for the tests from 1,905 boys, almost 90 per cent of the enrollment. As a result of our examinations 8 cases of chronic pulmonary tuberculosis were found. All but 3 of these cases were minimal in extent. One moderately advanced case had a positive sputum. Most of the boys are now under treatment. The ages of the cases were widely distributed, three being 15 years of age, three 18, one 19 and one 20 years old. The incidence of manifest tuberculosis in this group was 0.4 per cent.

The third survey, in the Stuyvesant High School, was of a different character. Stuyvesant High School, located on the lower East Side of New York, draws its students from four boroughs of the city, and from

TABLE 2

Results of surveys in New York City high schools—1937

	NUMBER OF STUDENTS X-RAYED	NUMBER OF STUDENTS WITH ACTIVE TUBERCULOSIS
Wadleigh High School	1,635	14
Benjamin Franklin High School	1,905	8
Stuyvesant High School	2,785	2
Total	6,325	24

Bureau of Tuberculosis, Department of Health, New York City.

all racial groups. The school has a scientific and preprofessional curriculum, and the boys are of a higher economic level than those studied previously. Half of the school population was selected for X-ray examination, and one quarter of the entire school received the Mantoux test; 2,785 X-ray films were taken, representing 98 per cent of the group chosen for study. Two cases of chronic pulmonary tuberculosis of the reinfection type were found, one in a Negro and one in a white boy. Both were minimal in extent. One pupil was 16, the other 17 years old. The incidence of tuberculosis in this group was less than 0.1 per cent.

Our results in the three high schools, composed of adolescents 14 to 20 years of age, were as follows. The incidence of tuberculosis was 4 cases per thousand, made up of 14 cases in Negro, and 10 cases in white students. This represents a significantly higher incidence in the colored group, largely due to the preponderance of girls in the Negroes studied.

The girls showed a higher incidence than the boys, although the comparison is weighted by the difference in racial and economic groups. Most of the cases occurred at the 16, 17 and 18 year levels and were minimal in extent. The general morbidity rate was lower than that found in mass survey studies in adults. So far we are tempted to conclude that tuberculosis in the high school population is a much less serious problem than we had anticipated. We are not ready, however, to stop studying the adolescent group. Sixty-three hundred students is not a large enough sample of almost 350,000 high school pupils to warrant arriving at final conclusions. Further investigations, particularly in girls, and preferably in other portions of the city, are necessary and these are in progress. Moreover we are firmly convinced that these studies have proved of considerable educational value. The interest on the part of students and parents has been keen, and a consciousness of the tuberculosis problem and the necessity for X-ray examination has been aroused. This would seem sufficient justification for the continuance of a certain amount of this work in the high schools.

As regards methods, with an incidence of tuberculosis infection of less than 50 per cent, tuberculin testing and X-raying of positive reactors would appear to be indicated. Universal X-ray examination is a simpler procedure, however, and may be a more potent educational weapon. The roll paper method presents a rapid inexpensive type of roentgen examination, and we have utilized it in all of our high school work, taking the films right in the schools in almost all instances.

There remains for discussion our case-finding experiences in the major field of our activity, the adult population. Any very complete examination of this group has, of course, been impossible. We have been forced to confine our mass survey studies to those portions of the populace that lent themselves to this type of work, choosing the groups where our efforts were most apt to be productive.

One large group recently studied is the applicants for employment in the Fire Department of the City of New York. For the past fifteen months all eligibles for this service have had a chest X-ray before acceptance. As a result we have now studied 1,964 candidates. These have all been young adult males in good health and of fine physical development. They have passed the strenuous physical tests which constitute part of the requirements for the Fire Department, and have been subjected to a complete medical examination, in which no serious abnormalities have been found. Yet almost 2 per cent of this carefully

selected group have had tuberculosis, in two-thirds of whom it was active. Another 2 per cent required further observation before tuberculosis could be ruled out. One applicant in 24 has shown a pulmonary lesion on the X-ray film.

Turning to the applicants for employment in the Health Department, we again find ourselves dealing with a selected group. These candidates had also passed a medical examination, but had been subjected to much less strenuous physical tests. The group was a mixed one, females predominating. All were presumably in good health, yet of the 667 routinely X-rayed, 6.9 per cent were found to have tuberculosis, 2.2 per cent in an active phase, and an additional 2.4 per cent are under observation as suspicious cases. One individual in 9 has shown some parenchymal lesion on the X-ray film.

More recently we have studied a small group of 100 applicants for

TABLE 3

Results of surveys of applicants for employment, New York City, 1936–1937

	NUMBER X-RAYED	PER CENT WITH ACTIVE TUBERCULOSIS	PER CENT WITH ARRESTED TUBERCULOSIS	PER CENT WITH NON-TUBERCULOUS PATHOLOGY	PER CENT FOR OBSERVATION
Fire Department	1,964	1.3	0.5	0.4	2.0
Health Department	667	2.2	4.7	2.2	2.4
Guides	100	2.0	6.0		4.0

Bureau of Tuberculosis, Department of Health, New York City.

employment as guides. These were all older men, not subject to medical or physical examination, but all apparently in good health. Eight per cent showed evidence of tuberculosis by X-ray, 2 per cent being classified as active. An additional 4 per cent fell into the observation category. In this group one in eight has shown evidence of pulmonary disease on X-ray.

These three groups were made up of individuals whom we X-rayed as part of preëmployment requirements. No attempt was made to select them as susceptibles or likely subjects for case-finding surveys. In fact, the applicants for the Fire Department were probably the furthest from that category of any group we might have chosen, yet almost 2 per cent had active tuberculosis. What would we find in groups and areas where tuberculosis is more apt to be prevalent? Our mass survey studies in Harlem have partly supplied the answer.

In August, 1935, in coöperation with the State Temporary Emergency

Relief Administration, the Department of Health started its survey in East Harlem, the centre of New York City's Porto Rican population. The inhabitants of this region on the Home Relief rolls were given routine X-ray examination, having been persuaded to report to the clinic by a staff of field investigators assigned to the project. All X-rays were taken on celluloid film. During the following twelve months, 3,214 individuals were examined; 207 were found to have tuberculosis, almost 60 per cent in an active form. This is an incidence of 3.7 per cent active tuberculosis, almost twice that found in the applicants for employment previously discussed. This is a group of susceptibles from the racial and economic point of view, but a group all presumably in good health. A recent recheck in one health area in this district has shown confirmatory findings, the incidence of disease less than two years later being almost 12 per cent. If we allow for the fact that the more seriously ill portion of the populace was either at home, too ill to report for examination, or already hospitalized, the magnitude of the tuberculosis problem among the Porto Ricans of New York City assumes staggering proportions.

The next group requiring this type of investigation, from the point of view of susceptibility, is the Negro population. Their mortality rate, although not as high as the Porto Rican, which in some districts is twelve times that of the white population, still exceeds the white rate by 500 per cent. Although the Negro constitutes only 5 per cent of the population of this city, he furnishes 22 per cent of the annual deaths from tuberculosis. Our mass survey was started in Lower Harlem in December, 1936. Again we confined our efforts to people on the Home Relief rolls, employing the services of a staff of home investigators. Individuals were referred to the Lower Harlem Chest Clinic, where the roentgenograms were taken and read. Paper films, checked on celluloid, were used. By the end of 1937 almost 40,000 individuals had been studied in this manner. About 750 have been found to have tuberculosis; an incidence of 2 per cent in a group large enough to be representative. We believe this estimate is low, as the previously mentioned factors were certainly operative. The coöperation of this group was considerably poorer, and those of its members most in need of care probably never reached us. In addition, the more violent nature of the disease in the Negro undoubtedly necessitated immediate hospitalization in a considerable number that we otherwise might have examined.

Other, less recent, studies made by this Department in coöperation with the State Temporary Emergency Relief Administration, the Association for Improving the Conditions of the Poor, the Milbank Memorial

Fund and the National Tuberculosis Association have shown similar findings. These will not be discussed in detail as they have been reported previously. Among those examined by the mass survey method were groups on home relief in the Red Hook-Gowanus section of Brooklyn (3) and the Lower West Side of New York, and several thousand food handlers throughout the city (4). In all, over 100,000 individuals have been X-rayed in mass survey studies. In this large body of apparently healthy people the incidence of active tuberculosis has been over 2 per cent, and in susceptible racial and economic groups has exceeded 6 per cent. The tuberculosis found in this way has been discovered early, 75 per cent of our cases falling into the minimal classification. All of these cases were found in individuals presenting no symptoms, who would not have otherwise sought medical attention, and hence had to be approached by the doctor going to the patient, rather than the time honored reverse. This large group differs from most of the cases

TABLE 4

Results of surveys of individuals on home relief New York City, 1935–1936–1937

	NUMBER X-RAYED	NUMBER FOUND TUBERCULOUS	PER CENT
Meinhard	3,214	207	6.4
Lower Harlem	38,456	756	2.0

Bureau of Tuberculosis, Department of Health, New York City.

examined by this Department who come to us because of symptoms, either directly or referred by their physician, or because of contact with an open case of tuberculosis. The latter are examined through our regular clinic services, which are operated in the traditional way on a city wide basis. Fifty-eight thousand such individuals were seen in this manner last year, 7.6 per cent of whom were found to have tuberculosis. Our growing volume of survey work is directed toward the former, and by far the larger group, the apparently healthy adult.

Mass surveys are only possible through the use of a convenient, relatively inexpensive, and technically satisfactory method of examining large groups of people by X-ray. The rapid roll paper method meets all these requirements and we have utilized it in almost all of this work.

Finally, we have realized with increasing clearness that we have just scratched the surface in this vast field. Other groups must be studied, and our work in those already under study must be continued and expanded. Homeless lodging-house dwellers, prisoners, industrial workers,

college students are but a few of the segments of the populace that should be surveyed as part of the case-finding program. Some of these studies are in progress, others in prospect. When they have been concluded we may be in a position to answer the questions, where shall we look, when shall we look, and how shall we look for tuberculosis.

SUMMARY

1. The major portion of the tuberculosis control program of the Bureau of Tuberculosis of the Department of Health of New York City is devoted to case-finding, although an effort is made to maintain a constant balance between case-finding and case-supervision.

2. The case-finding policy of this Bureau is based on the search for tuberculosis in the groups where it is most apt to be found, at the time when it is most likely to be discovered in its incipiency.

3. The preadolescent child is not a fertile field for case-finding by the mass survey method. A study of 9,500 children, 3 to 16 years of age, investigated by tuberculin test screening and X-ray of the positive reactors revealed only two cases of reinfection tuberculosis.

4. The incidence of active tuberculosis of the reinfection type in 6,300 high school students in New York City was 0.4 per cent, the majority of the cases occurring in female Negroes and at the 16, 17 and 18 year levels. Tuberculin test screening and universal X-ray examination are both valuable mass survey methods at this age.

5. The major field for mass case-finding should be the adult population. Routine X-ray examination of over 100,000 apparently healthy adults has revealed two to twelve per cent with tuberculosis, half of which has been clinically active. The highest incidence has occurred in susceptible racial and economic groups. These cases have all been discovered in individuals with no symptoms of pulmonary disease.

6. The method of choice for mass survey studies in the adult population is the rapid roll paper method. It is convenient, relatively inexpensive and technically satisfactory for this work.

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RESULTS OF TREATMENT OF TUBERCULOSIS IN THE NEGRO [1,2]

G. D. KETTELKAMP, PAUL MURPHY AND DARRELL TRUMPE

Not many years ago the opinion was almost universal that the Negro race was lacking in natural resistance to tuberculosis, and that once Negroes were attacked by the disease, their chances of recovery were almost nil. McCain (1) in a recent paper states: "In 1920 during the discussion of one of the earlier papers on tuberculosis among Negroes, presented before the National Tuberculosis Association, one physician stated that whenever he heard of a Negro recovering from tuberculosis he considered that there had been a mistake in diagnosis." In recent years much thought and study have been given this subject, and more and more evidence is coming to light to show that tuberculosis in the Negro is not the hopeless condition it was formerly thought to be.

In this study we have confined ourselves to an effort to determine how the Negro responds to sanatorium treatment. While environmental conditions in the institution are similar for the two races, it must be remembered that influences of heredity and environment which prevailed before admission to the institution carry on and exert their influence after admission to the hospital. The Negroes admitted to Robert Koch Hospital come from a poorer environment than do the white patients, who represent the usual classes commonly encountered in the municipal hospitals of large cities. Comparatively few of our Negroes are native-born St. Louisans. The majority came from Mississippi, Missouri, Arkansas, and Tennessee. About 90 per cent of them were born in what were formerly slave states.

From 1922 to 1936 inclusive, the Negroes have comprised, on the average, 11 per cent of the St. Louis population. For this same period the Negroes' mortality from tuberculosis has averaged 313 per 100,000, as against 63 for the whites. It is obvious what a tremendous problem this presents.

[1] From Robert Koch Hospital, Hospital Division, Department of Public Welfare, St. Louis, Missouri.

[2] Read at the Mississippi Valley Conference on Tuberculosis, Dayton, Ohio, September 23, 1937.

Its magnitude is further increased when we consider that the Negro's occupation is usually one which brings him into intimate contact with other people, both colored and white. Many Negroes, particularly the women, take care of small children. A recent survey revealed that roughly 80 per cent of our female Negroes and 30 per cent of the males had worked under circumstances which afforded more than average chances for them to infect other people.

The results of treating tuberculosis in the Negro assume added significance when compared with the results obtained in white patients under essentially the same circumstances. For this reason, we are presenting the end results obtained in two series of 1,000 consecutive discharges from Robert Koch Hospital.

This institution has 500 beds, approximately 125 of them for Negroes. All types and stages of tuberculosis are treated and all beds are free. It is necessary to say a few words about how our patients are admitted.

The vast majority of men enter from the white or Negro City hospitals. The Isolation Hospital has beds for 67 females who are awaiting admission to our sanatorium, and most of our females are admitted from there. A few patients enter from private hospitals or directly from home treatment. In recent years, our waiting list has averaged about 225, so it is obvious that the patients we admit have been, as a rule, under some sort of medical care for a period varying from a few weeks up to possibly eight or nine months. During the time when the first 1,000 patients were discharged, this waiting list was not as long, averaging perhaps between 100 and 150, and hence the interval between the time of diagnosis and the patient's admission to the sanatorium was appreciably shorter. This accounts, in part at least, for the fact that our first 1,000 discharged cases were much the sicker on admission, as judged by the severity of their symptoms. As will be emphasized later, there is a factor of selective admissions in regard to the female patients, both Negro and white, who enter from Isolation Hospital. Those requiring surgical collapse are given preference.

With an exceedingly rare exception, all female patients at Isolation Hospital, except those who die there or leave against advice, eventually come to Robert Koch Hospital to complete their cure.

The first series consists of the 1,000 patients discharged between November, 1922 and April, 1926. The second series is composed of the 1,000 cases discharged between April, 1933 and April, 1937. We are concerning ourselves mainly with pulmonary tuberculosis. For various

reasons a comparison of the complications, both tuberculous and nontuberculous, was not feasible. It is our impression that tuberculous complications present the same problem in the Negro as in the white. In regard to nontuberculous complications, the chief difference we have noted is the much higher incidence of syphilis in the Negroes; we are uncertain, however, how much effect this disease has on their tuberculosis.

We have not noted any definite manifestations of tuberculosis peculiar to the Negro. It all looks much the same to us except the color of the patient's skin. In a general way, the Negro seems to maintain a better state of nutrition and muscular tone unless he is very toxic. We are prone to attribute their better nutrition to their lack of worry. When doing well, they seem to have a tendency to show more lymphocytes in their differential blood counts than do white adults in a similar state of recovery.

In our experience there is little difference between the Negroes' and the whites' ability to adjust to the sanatorium environment. We have found the Negro very amenable to the routine and discipline.

In the following tables we have attempted to present our material in statistical form. With rare exceptions, fractions of one per cent are designated by a plus or minus sign; consequently, the totals sometimes vary slightly from 100 per cent.

Table 1 shows the ratio of Negroes to whites and of males to females in the first and last 1,000 discharged cases. Note that the Negro to white ratio as well as the sex distribution is practically the same for these two series of discharged cases.

Table 2 shows the average age of the patients at the time of admission. The whites averaged older than the Negroes, and the males older than the females.

Table 3 shows the average number of hospital days. It will be noted that there has been a tremendous increase in the hospital stay for all groups, but that this increase is relatively greater for the Negroes. It is significant that the females of both sexes averaged a longer hospital stay than did the males.

Table 4 gives the classification of the patients on their admission to the hospital. An analysis of this table reveals the discouraging fact that in general our patients admitted within the past few years were as far advanced as those entering seven to fifteen years ago. Considering this from the standpoint of race, one sees no essential change for the whites. The Negro group shows appreciable improvement, however, and in the

TABLE 1

Percentages of races and sexes

FIRST 1,000 DISCHARGES				LAST 1,000 DISCHARGES			
Whites		Negroes		Whites		Negroes	
736		264		782		218	
Male	Female	Male	Female	Male	Female	Male	Female
64+	36−	52−	48+	61−	39+	52+	48−

TABLE 2

Average ages of patients on admission

FIRST 1,000 DISCHARGES						LAST 1,000 DISCHARGES					
Male		Female		Total		Male		Female		Total	
White	Negro	White	Negro	White	Negro	White	Negro	White	Negro	White	Negro
41	30	27	26	36	28	39	35	31	26	36	31

TABLE 3

Average number of hospital days

FIRST 1,000 DISCHARGES						LAST 1,000 DISCHARGES					
Male		Female		Total		Male		Female		Total	
White	Negro	White	Negro	White	Negro	White	Negro	White	Negro	White	Negro
225	98	211	131	220	125	575	471	729	515	635	489

TABLE 4

Classification on admission in percentages

	FIRST 1,000 DISCHARGES						LAST 1,000 DISCHARGES					
	Male		Female		Total		Male		Female		Total	
	White	Negro	White	Negro	White	Negro	White	Negro	White	Negro	White	Negro
Far advanced	77	67+	67	82	73	74	79	70	62−	62−	72	66
Moderately advanced	18−	20	20	6+	19	13	15−	13−	24+	20+	18	16
Minimal	4−	3−	9	2−	6	2	1+	1−	9+	7−	5	3+
Extrapulmonary	1+	10−	2−	8+	1	9	2+	8	1+	2+	2	5+
Childhood type	0.2	0	1+	2−	0.5	1	3−	9−	3+	7−	3	8+

last 1,000 discharged cases Negroes had fewer far advanced admissions than the whites. The drop in far advanced admissions for Negro females from 82 per cent to 62 per cent is especially noteworthy.

Table 5 gives the classification of the patients on the basis of the severity of their symptoms on admission, according to the National Tuberculosis Association standards. As a whole, the last 1,000 discharged cases were not nearly as sick upon admission as were the patients in the first 1,000 discharges. We feel our present larger waiting list which results in longer preliminary treatment, either in another hospital or at home before admission to Robert Koch Hospital, is largely responsible for this change. Again the improvement was relatively much greater for the Negro race, although they still are considerably more toxic on admission than the whites.

TABLE 5

Severity of symptoms on admission in percentages

	FIRST 1,000 DISCHARGES						LAST 1,000 DISCHARGES					
	Male		Female		Total		Male		Female		Total	
	White	Negro	White	Negro	White	Negro	White	Negro	White	Negro	White	Negro
Group 1	12+	3+	17+	1−	14	2	30−	24	35	30−	33	29
Group 2	30−	13	21−	11+	29	12	32	23	41+	18−	34	23
Group 3	60−	84−	53−	89	58	87	39	53−	22	54−	33	49

TABLE 6

*Pulmonary collapse therapy in percentages**

FIRST 1,000 DISCHARGES						LAST 1,000 DISCHARGES					
Male		Female		Total		Male		Female		Total	
White	Negro	White	Negro	White	Negro	White	Negro	White	Negro	White	Negro
1+	1−	1+	1−	1+	1−	30−	21−	51+	44+	38	30

* Includes all types and whether successful or not.

Table 6 deals with pulmonary collapse. Since the failures are included, it really represents the percentage of cases in which collapse therapy was indicated. The increase in this form of treatment during the past decade or more has been very great, and probably is the biggest factor in the improved results we have obtained in the treatment of pulmonary tuberculosis in both Negro and white. In considering the last 1,000 discharges one notes the percentage of females receiving collapse therapy was much greater than that of the males. Unquestionably more of our females are suitable for collapse therapy than are males, but not

to the degree the table indicates because of a selective factor at work. As has been previously pointed out, most of our females, both Negro and white, are admitted from Isolation Hospital, and those women needing collapse therapy other than pneumothorax are given preference when transfers can be made.

Table 7 shows the condition of the patients at discharge. It is evident that, as a group, the whites leave the hospital in better condition than do the Negroes. The margin of difference is not great, however, and comparing the results obtained in the first and last 1,000 discharged cases one notes that the degree of improvement has been greater in the Negro than in the white. Again the Negro female group shows the greatest relative improvement.

TABLE 7

Condition at discharge in percentages

	FIRST 1,000 DISCHARGES						LAST 1,000 DISCHARGES					
	Male		Female		Total		Male		Female		Total	
	White	Negro	White	Negro	White	Negro	White	Negro	White	Negro	White	Negro
Apparently healed	0.2	0	1−	2−	0.4	0.8	3−	8	3−	9−	3−	9−
Arrested	6	0	6−	2−	6−	0.8	17−	12	30+	25	22+	17+
Apparently arrested	0.6	0	2−	0	1−	0	1	0	3+	1+	2−	0.5
Quiescent	2	0	3−	1−	2	0.16	1	2	7−	4+	3	3−
Improved	20	15	23+	6+	21	11	21+	11+	20	15+	21−	13−
Unimproved	22+	26+	30−	19−	25−	23+	17+	18+	15−	13+	16+	16
Dead	50−	58−	36+	70+	45	64	38+	49	22−	32+	33−	41

A careful study of this table reveals that in the first 1,000 discharged cases the results were obtained on the basis of race. Listing the race and sex groups according to the desirability of the end results obtained, gives the following order:

White female
White male
Negro male
Negro female

In the last 1,000 discharged cases this order changes to:

White female
Negro female
White male
Negro male

It shows that the results were obtained, not on the basis of race, but of sex, with females having all the better of it. We shall not devote space as to the possible reason for this, but in passing it may not be amiss to point out that, as a group, the females have a longer hospital stay, show a higher percentage suitable for collapse therapy, and apply themselves more diligently to the "task of curing" than do the males.

In this study we want to emphasize particularly the results obtained in the Negro compared with the white. Evaluating our statistics as a whole from this point of view, it is seen that the white still achieves a better end result than the Negro, but that of recent years this margin is narrowing to such an extent that it has little significance. Furthermore, considering the fact that the Negro had much severer symptoms on admission than the white, leads us to conclude that, despite a slightly poorer end result, the Negro group derived as much, if not more, benefit from hospital care than the white. Since this situation did not pertain in the first 1,000 discharged cases, it is evident that the last seven to fifteen years has brought about a decided improvement in the results obtained from sanatorium care in the Negro. Furthermore, the degree of this improvement is considerably greater than that shown in the results obtained in treating white patients during the same period of time.

The reasons for this are not clear. In all probability many different factors are involved which are so hopelessly intertwined as to defy analysis. The one thing, however, with which we in St. Louis have been impressed is that within the last decade our Negro population has assumed a very different attitude toward their tuberculosis problem. No longer are they indifferent or fatalistic to it. On the contrary, there seems to be a widespread appreciation of the modern methods of combating tuberculosis and a willingness to avail themselves of all the opportunities afforded them for combating this disease which is one of the greatest health problems with which their race must contend.

SUMMARY

1. We found no essential difference in the anatomical classification of disease between Negroes and whites on admission.

2. The Negroes had severer symptoms on admission than did the whites.

3. Negro males showed a less desirable end result after their hospital stay than did white males. Negro females showed a less desirable end

result than did white females. But Negro females showed a more desirable end result than white males.

4. In the first 1,000 discharges our results seem to have been obtained on the basis of race. In the last 1,000 discharges, occurring seven to fifteen years later, the results seemed to rest not on the basis of race but of sex.

5. We noted no essential difference in the behavior of tuberculosis in the Negro from that in the white.

6. The Negroes are amenable to sanatorium treatment in all its phases, and, considering all factors, we feel they derive at least as much, and possibly more, benefit from it than do the whites.

REFERENCE

(1) McCain, P. P.: Tuberculosis among Negroes in the United States, Amer. Rev. Tuberc., 1937, *35*, 25.

THE ANAEMIA OF PULMONARY TUBERCULOSIS

MORRIS M. BRAVERMAN[1, 2]

It is interesting to note that much work has been done on the white blood cell picture and sedimentation rate in tuberculous patients while but scant attention has been paid to the erythrocytes and anaemia and to the bone marrow in such people. In an effort to learn more about these questions the blood was studied routinely and bone marrow was obtained from patients during thoracoplasties and from autopsied patients in about 100 cases. It is obvious that pulmonary tuberculosis lends itself to a study of the bone marrow and of anaemia.

MATERIAL

The 509 patients were divided into two groups, males (221, or 43.3 per cent) and females (288, or 56.5 per cent). These were further classified into minimal (49, or 9.6 per cent), moderately advanced (79, or 15.5 per cent) and far advanced (381, or 74.8 per cent) pulmonary tuberculosis according to the classification of the National Tuberculosis Association. Most of the patients were from Middlesex County Sanatorium in Massachusetts and the rest from Herman Kiefer Hospital and Wm. H. Maybury Sanatorium in Michigan.

Bone marrow sections were obtained in about 100 of the tuberculous individuals who came to thoracoplasty, paraffin pack or autopsy. This was a routine during the period from April, 1934 to September, 1936.

Of the 509 patients, 371, or 72.8 per cent, had sputum containing tubercle bacilli.

Many complications were discovered among the tuberculous patients. Some were diagnosed during life and others at autopsy or on microscopical examination of the tissues. It is not pertinent to list all the complications since many are not germane. The more important ones are: intestinal tuberculosis in 66 of the 509, or 12.9 per cent (autopsy); pleurisy with

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effusion, presumably tuberculous, in 29, or 6.2 per cent; tuberculous empyema in 24, or 5.1 per cent; laryngeal tuberculosis in 27, or 5.7 per cent; miliary tuberculosis in 9, or 1.9 per cent; amyloid disease in 8, or 1.7 per cent; diabetes mellitus in 8, or 1.7 per cent; tertiary syphilis in 7, or 1.5 per cent; pernicious anaemia in 2, or 0.4 per cent; and Addison's disease in 1, or 0.2 per cent. The figures for intestinal tuberculosis seem low but nevertheless in the early years of the sanatorium the complication was found in 100 per cent of all the far advanced patients autopsied. The diagnosis of Addison's disease was confirmed by post-mortem examination.

METHODS

The 509 patients were studied from October, 1931 to October, 1936. In all but the first 45 of these during the period from October, 1931 to November, 1933 certified apparatus was used and a careful technique followed. The following procedures were done: red and white cell counts, haemoglobin determination by Sahli, differential count, sedimentation of red cells and icterus index. None of the counts during the first period were duplicated.

After November, 1933 and up to October, 1936 the red and white cell pipettes and the Levy-Hausser counting chamber with improved Neubauer double ruling were certified by the U. S. Bureau of Standards. Wintrobe haematocrit sedimentation tubes (1) were used. Blood smears were made on cover slips, mounted on slides and filed.

During the first period the blood sample was usually capillary from the ear. One red and one white pipette were filled. A haemoglobin determination (Sahli) was done at the bedside. One hundred white cells were counted for the differential.

During the second period from November, 1933 to October, 1936, most of the determinations were on venous blood. Five cc. were obtained without stasis from an anterior cubital vein. The venous blood was collected in dry, clean syringes, placed in small bottles containing 0.05 cc. of a 20 per cent solution of potassium oxalate and carefully agitated. The oxalated blood was allowed to stand at room temperature for at least a half hour and all the determinations including the sedimentation were started within three hours after withdrawal of the blood. Two red and two white blood cell pipettes were used for each determination. Figures for the red cells agreeing within 250,000 per cmm. were accepted; often the check was around 100,000, or less. For the white

blood cells the accepted figures usually agreed within 200 to 300 cells per cmm. One determination was made for the haemoglobin by Sahli's method in grams and per cent; most of the readings were done during daylight. The blood in the haemoglobin determination was added to $\frac{1}{10}$ normal hydrochloric acid, mixed and allowed to stand for ten minutes. The blood for the differential count was obtained either from the finger or ear or vein; usually it was the former.

The red cell sedimentation (Wintrobe (1)) was read from the left hand scale in mm. every five minutes up to one hour and rarely to seventy-five minutes. A larger amount of venous blood was withdrawn when necessary for Wassermann, Hinton, Kahn tests or blood chemistry studies.

All Sahli haemoglobin tubes and appropriate pipettes were checked by the Van Slyke oxygen-capacity method and proper corrections made for each. For the Sahli tubes the original uncorrected figure was 17.00 grams of haemoglobin per 100 cc. of blood. This actually varies from 17.00 to 17.60. It should not be surprising that Sahli haemoglobin pipettes vary in bore and necessitate corrections from 0 to 5 per cent; 15.63 gm. of haemoglobin per 100 cc. of blood was accepted as equivalent to 100 per cent. Charts were made to correct our Sahli haemoglobin tube readings to the accepted 15.63 scale of 100 per cent.

When the sedimentation of the red cells was completed the previously stoppered Wintrobe tube was centrifugalized for thirty minutes at 3,000 r.p.m. Complete packing of the cells is obtained (2). The volume or haematocrit per cent of the red cells was read off directly from the right hand scale after first allowing the tube and contents to stand for about one-half hour at room temperature. Because of shrinkage due to potassium oxalate, the haemotocrit per cent was multiplied by the factor 1.09.

A graph of the sedimentation fall in mm. for every five minutes was constructed and the red cell sedimentation speed calculated in mm. per minute. The sedimentation rate was corrected according to its haematocrit per cent (3). Thus, there is a correction for the red cell size and number. The Wintrobe tube is then placed in a comparator and the icterus index value noted.

In most cases all blood samples were obtained under basal conditions (9 to 11 a.m.).

Those patients who received liver extract or some form of iron had blood studies once a month and about 50 had counts every two weeks.

Gastric analyses were done on only 3 patients. The test meal consisted of a glass of water and a slice of bread. Samples of gastric juice were withdrawn thirty and forty-five minutes after ingestion and compared with the fasting specimen.

Studies on the bone marrow, "activity" in pulmonary tuberculosis and bilateral simultaneous venous blood counts and venous blood pressure determinations will be reported upon later.

Only those patients who had the appropriate laboratory data are considered in any of the tables.

NORMAL VALUES AND CALCULATIONS

The following normal values and calculations are based on venous whole blood. The normal range of the erythrocytes as reported by Wintrobe (4) and by Osgood (5) are identical. For males between the ages of 14 to 30 years the average is 5,400,000 and the range 4,600,000 to 6,200,000. For females of the same age group the mean is 4,800,000 and the range 4,200,000 to 5,400,000.

One hundred per cent of haemoglobin is considered as equivalent to to 15.63 grams per 100 cc. of blood (6). The 17.00 grams of haemoglobin per 100 cc. of blood (100 per cent) as indicated on the Sahli tube by the manufacturer is too high. The majority of investigators have accepted figures between 15.12 and 15.85 gm. (7) of haemoglobin per 100 cc. The normal range is from 13.26 to 14.82 or 85 to 95 per cent. Females often have values near the minimum of this range and the males near the maximum. The color index is 0.94 to 0.95.

The white cell range is from 6,000 to 9,000 per cmm. The differential is as follows: neutrophiles from 50 to 65 per cent, lymphocytes from 25 to 39 per cent, monocytes from 6 to 9 per cent, basophiles from 0.25 to 0.50 per cent, and eosinophiles 1 to 5 per cent. The monocyte-lymphocyte ratio (M-L) range is from 0.13 to 0.30.

The average haematocrit per cent of the red cells in females, as accepted by Osgood and Haskins (8), is 41 per cent, and the range for 90 per cent of the cases was from 37 to 45. They found the average for men to be 45 and, in 90 per cent of them, the range was from 40 to 50. These figures are practically identical with those published by Osgood (5). Wintrob (4) gave the following figures: men, average 47 cc. per 100 cc., with 40 to 54 cc. as the range; women, average 42 cc. and the range from 37 to 47 cc. For practical purposes these investigators agree and, as stated by Wintrobe (4), "there is no geographic variation in

normal blood values and no significant variation with age after adult life is reached."

There is a difference between the "sedimentation index" (S.I.) and the "sedimentation rate" (S.R.) of the red cells. The former refers to the distance measured in mm. that the upper level of the sedimenting red cells have fallen in a vertical tube at the end of given periods of time or usually up to 60 minutes. While the latter represents the rate of fall in mm. per minute of the top level of the red cells.

The S.I. at the end of one hour was found by Wintrobe and Landsberg

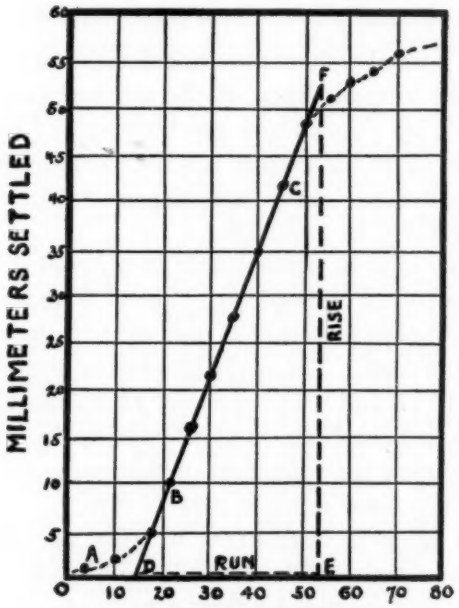


Figure 1

(9) to vary from 0 to 15 mm. Their average S.I. for healthy men at the end of one hour was 3.7 mm. and in normal women 9.6 mm. In 86 per cent of the men examined they found the S.I. to be from 0 to 6.5 mm. whereas in the same proportion of women the S.I. ranged from 0 to 15 mm. Furthermore, they state that in an additional 9 per cent the S.I. ranged as high as 9 mm. in men and 20 mm. in women. Their figure of 20 mm. cannot be accepted and it is believed our methods of diagnosis often do not discover the hidden cause.

If the sedimentation in mm. of the red cells is noted every five minutes

then a curve (figure 1) can be constructed by plotting the amount of settling against time. Rourke and Ernstene (3), at the suggestion of Wilson, utilized the middle phase of the sedimentation curve. This phase occurs invariably and is the one least influenced by aggregation and packing during sedimentation.

The obviously straight line portion of the sedimentation curve is extended downwards to the base line of the chart to a point D and upwards into the packing phase of the curve to any convenient point F. A perpendicular, FE, is dropped from the point F to the base line at E. The slope of the straight line portion of the curve is then $\frac{FE}{DE}$ and this represents the sedimentation speed measured in mm. per minute. It is another way of expressing the simple formula: S (speed) times T (time) = D (distance), or $S = \frac{D}{T}$.

The two most common factors affecting the S.R. are anaemia and infection. Correction for the former may be necessary before the severity of the infection is known. The corrected sedimentation rate (C.S.R.) is read directly from a chart prepared by Rourke and Ernstene (3) by using the uncorrected sedimentation rate and the haematocrit per cent.

Wintrobe and Landsberg (9) published a chart aiming at the simplified correction of the S.I. against the haematocrit per cent for the factor of anaemia. Though at variance with the method suggested by Rourke and Ernstene and the one used by us, it is nevertheless a time and labor saver in a busy office or laboratory.

The mean corpuscular volume (M.C.V.) of the packed red cells may be calculated (10, 11) from the following formula: $\frac{\text{haematocrit per cent} \times 10}{\text{red cells in mils/cmm.}}$ and the result expressed in cubic microns. The normal range for the corpuscular volume and the mean has been variously expressed by numerous authors. A few are as follows: Walters (7), from 82 to 107 and mean 96.5; Wintrobe (10) from 75 to 95 and mean 85; Wintrobe (11) from 80 to 94 and mean 87. The latter figures were taken.

The mean corpuscular haemoglobin (M.C.H.) may be calculated from the following formula: $\frac{\text{grams of haemoglobin/100 cc.} \times 10}{\text{red cells in mils/cmm.}}$ and the result expressed in micromicrograms ($\mu\,\mu$). The mean and range have been variously stated as follows: Wintrobe (11) mean 29.5 and range from

27 to 32; Walters (7) mean 31.4 and range from 25 to 37 based on 92 per cent of 100 men between the ages of 20 and 30; Haden mean 31.0 and Foster and Johnson mean 30.3 (7). The figures accepted for this study have been those of Wintrobe.

The mean corpuscular haemoglobin concentration (M.C.H.C.) is computed from the following formula: $\frac{\text{grams of haemoglobin/100 cc.} \times 100}{\text{haematocrit per cent}}$ and the result expressed in per cent. The figures published by Walters (7) are: range from 27.5 to 36.5 for 92 per cent of a group of 100 men, and mean 32.4; Haden's (7) mean is 33.7, Osgood's (7) mean is 33.9, Wintrobe (7) 36.6, and Foster and Johnson (7) 34.7. Wintrobe (11) published other figures stating the mean to be 35 and the range 33 to 38.

The icterus index (I.I.) range is 4 to 6 units. An abnormal figure is not considered until 10 to 12 is reached and there is corroborative evidence. The standards were made according to the technique of Murphy's modification of the Bernheim method (12).

VENOUS VERSUS CAPILLARY BLOOD STUDIES

Certain advantages are claimed for examination by both the venous and capillary methods. For routine or special studies of the haematological pictures in pulmonary tuberculosis, the venous specimen allows the greatest number of determinations with a minimum of effort. Many of the normal values which have been published of late have been more carefully standardized on venous blood. The investigations of Wintrobe (2) and others revealed no regular difference between the cell counts and haemoglobin determinations made on blood taken from the vein and the finger pulp. A careful study of mine on 8 patients led to the same conclusions.

The advantages claimed by Wintrobe (1), and Osgood, Haskins and Trotman (13) regarding the use of venous blood are worthy of note. The following examinations may be done on 5 to 20 cc. of venous blood: Wassermann, Kahn or Hinton, red and white blood corpuscle counts, haemoglobin by Sahli, white cell differential count, sedimentation of the red cells, volume per cent or haematocrit of the latter, calculation of the mean corpuscular volume or mean corpuscular haemoglobin or mean corpuscular haemoglobin concentration, icterus index, blood chemistry determinations or any number of procedures in the diagnosis of a possible dyscrasia. As a result of both studies it is concluded that the venous

method has advantages over the capillary. Briefly they are: (*1*) greater accuracy in counts is possible with larger volumes of blood, (*2*) duplicate examinations in research work or in cases of error can be had without a repeated venipuncture, (*3*) the larger number of determinations possible on a single specimen obtained by seeing the patient once and (*4*) lack of need of bedside speed. No patient will object seriously to venipuncture, if it is universally employed in a sanatorium.

For subsequent examinations not all of the above determinations need to be repeated. It was noted that time can be saved by not repeating the red cell count and haemoglobin determination if the haematocrit per cent remains about the same. It may be taken for granted that the red cells and haemoglobin are about the same as before.

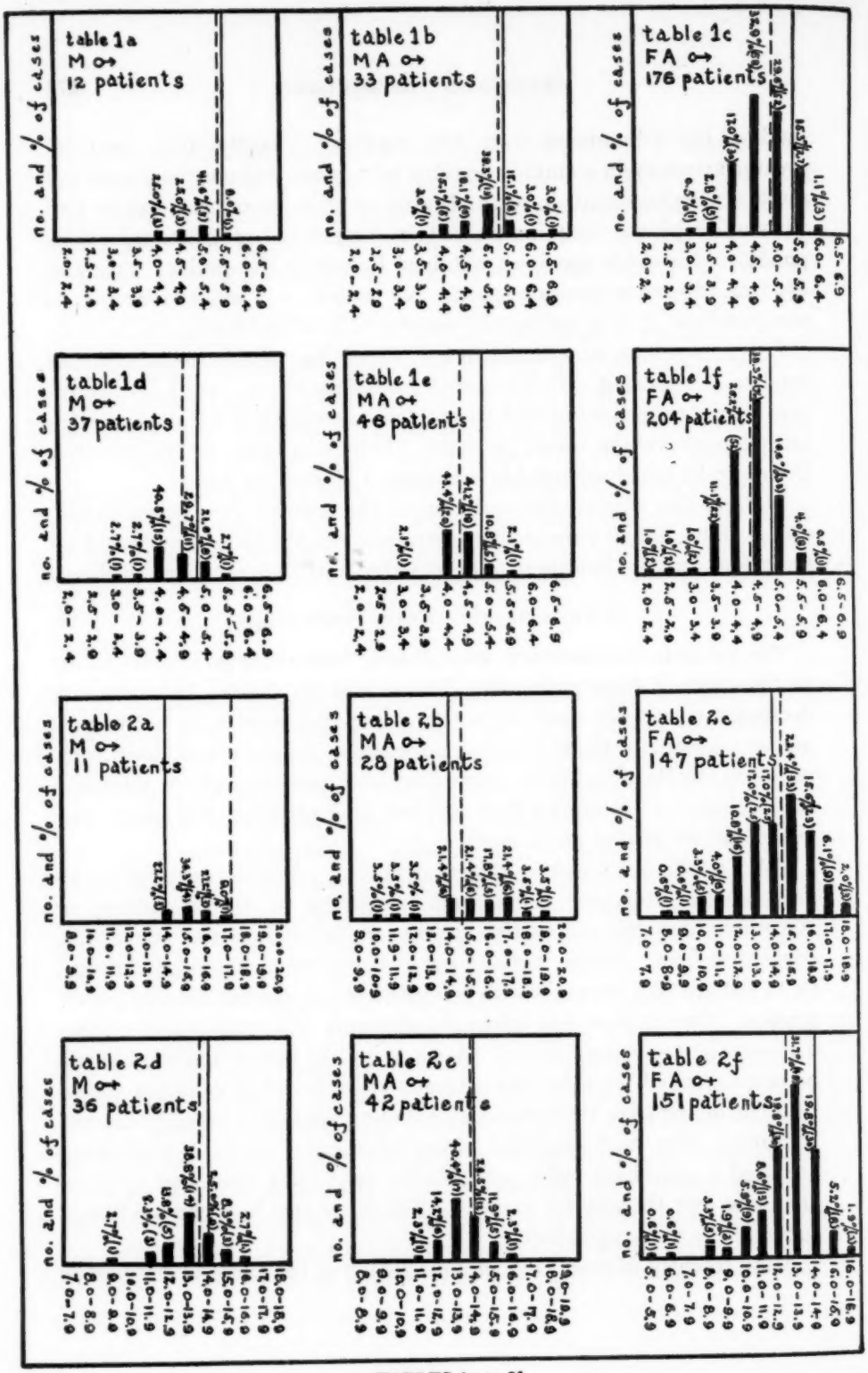
Walters (14) studied the variation of the erythrocytes, haemoglobin, etc. in immediately consecutive samples of venous blood and found no variations greater than those to be expected in chance random samplings.

NUMBER OF RED BLOOD CORPUSCLES

The patients on admission were divided into three groups according to the stage of their pulmonary disease and sex (tables 1a to 1f). A decreased count was most often found in patients with an active pulmonary lesion or those with a tuberculous or nontuberculous complication or those suffering from frequent haemoptyses or intestinal tuberculosis. It is known that bed-rest and adequate diet alone may lessen the severity of an anaemia.

Polyglobulia is not rare in clinical medicine. Among the usual causes are chronic pulmonary emphysema of asthma or fibroid phthisis or silicosis or bronchial obstruction, pulmonary arterial disease, anoxaemia, congenital heart disease, chronic passive congestion and high altitude. Of 11 patient (2.1 per cent) with polyglobulia not one had arterial hypertension. One of these had minimal pulmonary tuberculosis and another a moderately advanced lesion. A cause for the polyglobulia could not be demonstrated for these two patients and a better explanation should be forthcoming than their relatively small amount of pulmonary disease. The other nine were classified as far advanced. Seven of this group acquired a persistent mild polyglobulia only after they had received adequate iron therapy for months. The other two had chronic fibroid tuberculosis and emphysema.

More recently Molnar (15), in a discussion of the cause of circulatory



TABLES 1a to 2f

disturbances in pulmonary tuberculosis and a subsequent erythrocytosis, mentioned "circulatory decompensation and a decrease of the volume of the circulating blood." He believed that "pulmonary tuberculosis liberates histamin substances from the lung and these are responsible for a decrease of the circulating blood volume, diapedesis of plasma, decrease of arterial and venous pressure and finally erythrocytosis." No doubt it is inferred that anoxaemia plays its rôle, too. Magnusson (16) reported on the frequency of this manifestation in afebrile far advanced patients particularly the cyanotic ones.

QUANTITY OF HAEMOGLOBIN

For practical reasons it is best to express haemoglobin in grams per 100 cc. of whole blood rather than in per cent. It is confusing to read the reports of per cent of haemoglobin and omit the statement as to how many grams of haemoglobin are equivalent to 100 per cent. It is equally perplexing for the equivalent of 100 per cent of haemoglobin to vary from 12.0 to 17.6 grams per 100 cc. of blood.

The frequency distribution of haemoglobin in grams per 100 cc. and of the mean corpuscular haemoglobin concentration of all patients on admission to the sanatorium are expressed in tables 2 and 3. The stage of the disease and sex are factors determining the corpuscular haemoglobin. The factor of sex is more important in the female. The mean corpuscular haemoglobin concentration is regarded as a constant characteristic throughout normal life (17, 18).

The haemoglobin tables (in grams) indicate that about 20.0 per cent of all patients on admission, regardless of the stage of disease or sex, have figures below normal. Using the mean corpuscular haemoglobin concentration to reveal anaemia, table 3 indicates it in as many as 46.0 per cent of the patients. The mean corpuscular haemoglobin concentration takes into consideration the red cell count, their volume per cent, and the haemoglobin content of the mass of the red cells. A consideration of all these factors leads to a more accurate estimation than that gained by single factors.

TABLES 1a to 1f

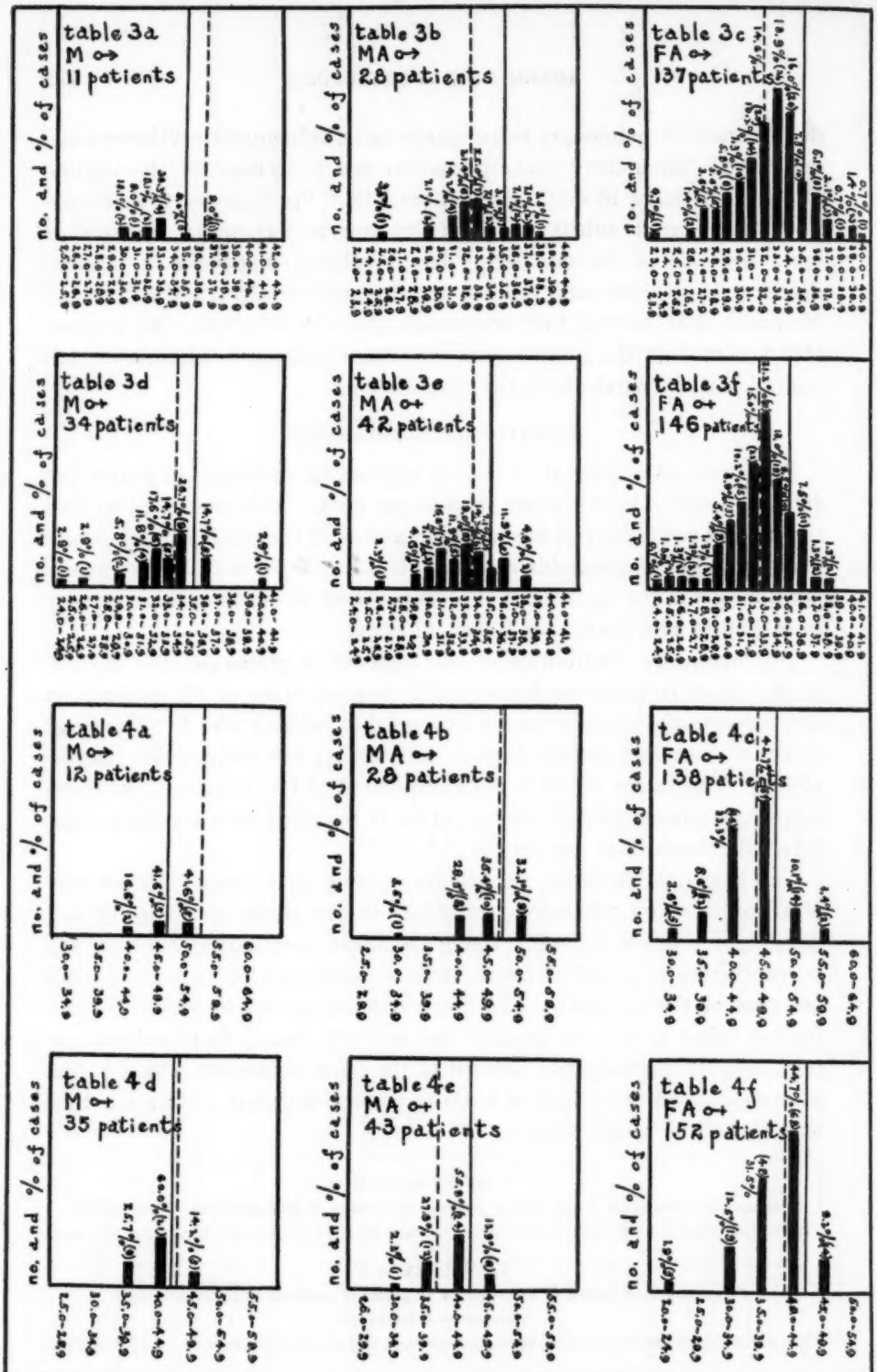
Frequency distribution of red cells of patients on admission with pulmonary tuberculosis

The narrow black line represents the normal average and the broken line the calculated mean

TABLES 2a to 2f

Frequency distribution of haemoglobin in grams of patients on admission with pulmonary tuberculosis

The narrow black line represents the normal average and the broken line the calculated mean



TABLES 3a to 4f

SIZE OF THE RED BLOOD CORPUSCLE

The volume per cent of the red cells or the haematocrit per cent and the mean corpuscular volume of the red cells are largely influenced by the stage and activity of the pulmonary disease. Other factors are chronicity of the lesion, sex, complicating or secondary nontuberculous infection, amyloid disease, various tuberculous complications, such as laryngeal, meningeal, intestinal, and bone and joint diseases and the adequacy of the diet.

The frequency distribution of the haematocrit per cent and the mean corpuscular volume for all the patients on admission to the sanatorium according to the stage of their disease and sex are expressed in tables 4 and 5. During the clinical course of the patient the frequency of microcytosis or normocytosis was largely dependent upon the activity or

TABLE 6

Incidence of the three common types of anaemia associated with pulmonary tuberculosis of 406 patients on admission

Normocytic Hypochromic Anemia – 42 patients or 10.3%						Microcytic Hypochromic Anemia – 61 patients or 15.0%						Microcytic Normochromic Anemia – 20 patients or 4.9%					
M		MA		FA		M		MA		FA		M		MA		FA	
♂→	♂←	♂→	♂←	♂→	♂←	♂→	♂←	♂→	♂←	♂→	♂←	♂→	♂←	♂→	♂←	♂→	♂←
0	3	2	2	22	13	1	2	1	1	16	40	0	1	1	1	9	8
0%	0.7%	0.4%	0.4%	5.4%	3.2%	0.2%	0.4%	0.2%	0.2%	3.9%	9.8%	0%	0.2%	0.2%	0.2%	2.2%	1.9%

quiescence of the pulmonary lesion or of its complications (table 6). Microcytosis was most often found in those patients exhibiting activity of their lesions. Pearl and Miner (19) were of the same opinion. It must be considered whether or not a patient is receiving iron because then the frequency of microcytosis (and hypochromia) decreases. Normocytosis reappeared less rapidly if bed-rest and collapse therapy alone were used.

TABLES 3a to 3f

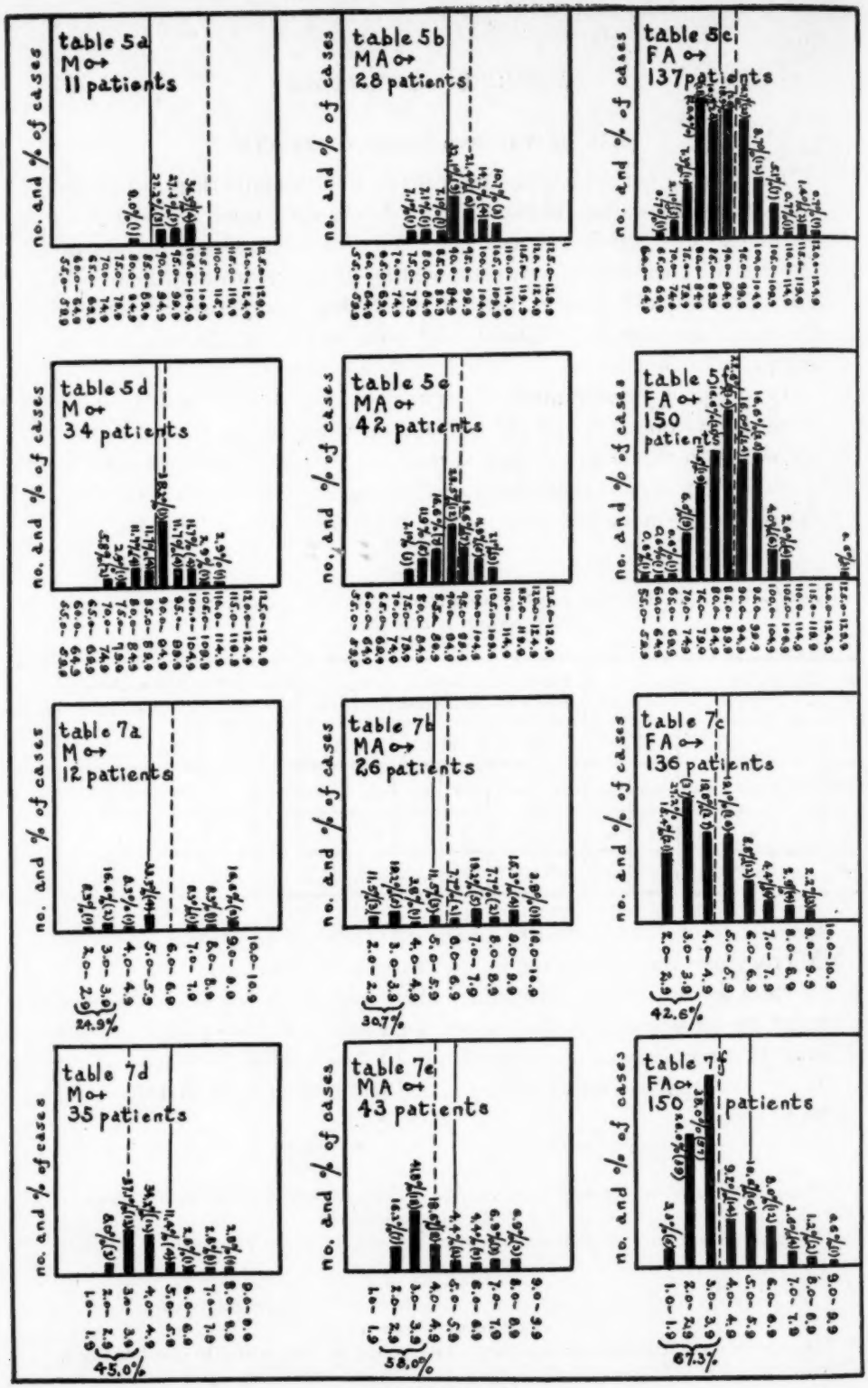
Frequency distribution of the mean corpuscular haemoglobin concentration of patients on admission with pulmonary tuberculosis

The narrow black line represents the normal average and the broken line the calculated mean

TABLES 4a to 4f

Frequency distribution of the volume or haematocrit per cent of patients on admission with pulmonary tuberculosis

The narrow black line represents the normal average and the broken line the calculated mean



TABLES 5a to 7f

Of the 509 patients in this study, there were 28, or 5.4 per cent, in the various stages of pulmonary tuberculosis with persistent hypertension. Many of these had systolic pressures over 150 and a few from 190 to 220. More than half of them had diastolic pressures of 100 or more. Twenty-four, or 85.7 per cent, had normocytosis and a normal mean corpuscular haemoglobin concentration. Of the remaining four, one had a macrocytosis and a slight hyperchromia while the other three had a mean corpuscular volume slightly above normal and a normal mean corpuscular haemoglobin concentration. Polyglobulia was not found among the 28 patients with hypertension. Doles (20) thought differently.

Perhaps the point may be raised that, since tuberculosis is a chronic infection and may be responsible for a diminution in the size of the red cells and/or hypochromia, any statement regarding the frequency of macrocytosis or hyperchromia in hypertensives is unreliable. It is noteworthy that activity of the lesions was largely absent or slight in this group of 28.

THE ANAEMIA OF PULMONARY TUBERCULOSIS

Microcytic hypochromic and normocytic hypochromic anaemia occur most often. During the early stages of the tuberculous lesion the first manifestation of anaemia may be hypochromia. Sooner or later microcytosis appears. Often the two are noted together if the infection is severe. Not infrequently microcytosis alone heralded the appearance of a more severe anaemia. The size and haemoglobin content of the red cells decrease as the severity and activity of the tuberculosis increase. Two patients (0.3 per cent) had a macrocytic hypochromic anaemia and were diagnosed pernicious anaemia.

Pulmonary tuberculosis is characterized by periods of stability, retrogression or progression. The frequency of anaemia and its character, therefore, vary according to the changing lesion. Complications have varied effects on the blood picture.

There were 871 sedimentation determinations on 412 patients. These

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TABLES 5a to 5f

Frequency distribution of the mean corpuscular volume of patients on admission with pulmonary tuberculosis

The narrow black line represents the normal average and the broken line the calculated mean

TABLES 7a to 7f

Frequency distribution of the icterus index of patients on admission with pulmonary tuberculosis

The narrow black line represents the normal average and the broken line the calculated mean

figures were corrected for the factor of anaemia, number and size of the red cells. For 838, or 96.2 per cent, of these the correction did not change their status as to normality or abnormality. The others, 33, or 3.8 per cent, were only slightly affected. The red cell count dropped to 2,400,000 and 2,900,000 in only 3 cases of severe haemoptyses. It appears hardly necessary in the routine study of most tuberculous patients to be concerned with the correction of the sedimentation rate for anaemia unless the anaemia is severe. Kaminsky and Davidson (21) found no definite relationship between variations in the number of red cells and sedimentation speed.

It has been incorrectly taught that most infections cause a destruction of red cells and haemoglobin. Robsheit-Robbins and Whipple (22) concluded "infection probably exerts an inhibitory action on the hematopoietic function by causing a disturbance of internal metabolism related to red cells and hemoglobin production." They claimed "infection does not interfere with intestinal absorption and subsequent storage of the products going to form hemoglobin, but does interfere with the orderly production of new hemoglobin." These facts appear to explain the normal icterus index range observed in about half of our patients and the low values in those with more advanced disease. Since circulating haemoglobin is often diminished in far advanced disease the occurrence of a greater than normal reduction of haemoglobin and the appearance of an elevated icterus index seem less likely.

Pallor in pulmonary tuberculosis was not found to be a reliable index of anaemia or of its severity. Labbe (23) attributed pallor mainly to a reduction of blood volume.

As already stated, anaemias may be classified (table 6) on the basis of size and haemoglobin content of the red cells. All patients with normochromic microcytic anaemia were treated with some form of iron by mouth. It is most probable that this group, too, would have had hypochromic microcytic anaemia had it not been for the iron therapy. The same is true of other measures of treatment which include bed-rest, adequate diet, and medical and surgical measures for the control of the pulmonary lesion or its complications. Considering all three types of anaemia most commonly encountered in pulmonary tuberculosis, anaemia (classified according to size and haemoglobin content of red cells) appears "statistically" as often as 30.2 per cent.

It is believed these figures do not reveal all the facts, and that anaemia occurs more frequently than these statistics indicate. Often it was

noted that a patient in the terminal stages of the disease, dehydrated, having diarrhoea, taking insufficient fluids or diet, would have a normal red cell count, haemoglobin, mean corpuscular volume and mean corpuscular haemoglobin. In such instances the blood would probably be different if we knew the values for the decreased blood volume and plasma and could make due allowances for dehydration.

It will be noted from tables 3a to 3f that the incidence of anaemia increases (46.0 per cent) with the mean corpuscular haemoglobin concentration as the basis of classification and calculations. The red cell count and the haemoglobin in grams per 100 cc. of blood do not always reveal an anaemia. The blood smear may be more instructive. More cases of anaemia will be uncovered by a consideration of all the data.

Macrocytosis was considered when the mean corpuscular volume was persistently 105 or over. In one patient on one occasion it was 122 but this was a technical error probably due to venous stasis. Two patients were diagnosed clinically as pernicious anaemia. One had a normochromic macrocytic anaemia and the other hyperchromia and macrocytosis. The incidence of the association of pernicious anaemia and pulmonary tuberculosis is slight. Barron (24) believed it to be so rare that its incidence is negligible.

Relatively few complications affect the blood picture in pulmonary tuberculosis. The blood picture is dependent on the state of the haematopoietic system prior to the onset of the additional disease. In terminal states it is not uncommon to find either a hypochromic microcytic anaemia or even a normal red cell picture throughout while the white cell count and differential and the sedimentation speed are indicative of acute massive infection and activity. The anaemia often becomes pronounced in the presence of intestinal tuberculosis and diarrhoea. This may not be the case if the diarrhoea is soon controlled and the patient receives iron by mouth. Schollenberger (25) found anaemia in about 80.0 per cent of 106 patients with pulmonary tuberculosis complicated by intestinal tuberculosis and that the latter is the most important factor in producing anaemia. Tertiary syphilis with an inactive pulmonary lesion may be accompanied by either a normal red cell count or a slight hypochromia. Diabetes mellitus was most often severe, occurred with extensive and progressive pulmonary tuberculosis and a moderate or severe hypochromic microcytic anaemia.

Taking into consideration all the complications, the anaemia often associated with them is hypochromic and microcytic and differs chiefly

in degree. If the acute pulmonary lesion is accompanied by sepsis, the severity of the anaemia increases rapidly. This is less marked in the case of amyloid disease. Complicating disease often reduces the blood from the lower limits of normal to that of a definite anaemia. Over 50 per cent of the patients with a significant complication had anaemia. Pregnancy occurred three times. One had a microcytic hypochromic anaemia and two were classed as normocytic hypochromic.

The criticism may be made that we should not group together on admission all the active and inactive patients, febrile and afebrile. However, it should be remembered that most of these patients on admission to the sanatorium had active lesions. To classify patients according to their febrile or afebrile state alone would result in a grouping together of various stages of the disease. Strict classification by any criterion is most difficult in pulmonary tuberculosis.

ICTERUS INDEX

There is every reason to believe that in pulmonary tuberculosis there is no increase in the normal rate of fragmentation of the red cells or reduction of haemoglobin. When the pulmonary lesion is sufficiently active either in severity or length of time, the first evidences in the peripheral blood will be a microcytic and/or hypochromic anaemia without an increase in the icterus index. Values below 4 units were noted in nearly half of all the patients on admission. This seems to reveal a strong tendency to conserve haemoglobin or an inhibition of its synthesis. Jaundice, when not due to obstruction in the biliary tract or to a haemolytic process, is not known in pulmonary tuberculosis.

Of the other 50.0 per cent only 11.3 per cent had figures between 8 to 10 units. Certain articles of food, namely carrots, eggs and oranges, lead to an increase of the I.I. A record was kept of the daily dietary of all patients. Most of the 11.3 per cent during the few hours preceding the withdrawal of the venous specimen had ingested either eggs or carrots or oranges. As for the others no satisfactory explanation was forthcoming.

Observations clinically and in the laboratory point to the belief that there is an inhibition of the metabolic processes which would ordinarily lead to a normal haematopoietic response and the formation of "icterus substances." Very frequently we have observed that, if the pulmonary disease becomes active or more active or advanced, the I.I. drops to either 4 or 3 or 2 units (table 7). This manifestation is more marked in

the female. This is true even when the red cell count and the haemoglobin values remain constant but the sedimentation increases steadily and there is the characteristic response of the white blood cells. These facts seem to indicate no actual blood destruction or haemolysis accompanying tuberculous infection or activity. Increasing I.I. values to 4 to 6 units or higher occur as the activity and amount of infection subside.

It is reasonable to suspect a possible hidden infection or have additional evidence that there is active infection if either a normal or abnormal red cell and/or white cell picture, abnormal sedimentation speed are present in the face of a low icterus index.

TREATMENT OF ANAEMIA

Multiple factors are often to be dealt with in chronic anaemia. The important measures in its treatment are (*1*) adequate control of the disease itself, (*2*) adequate diet, vitamin content and proteins especially fresh meats and (*3*) iron. Then, if the course of the pulmonary tuberculosis is favorable and uncomplicated the anaemia will usually subside in about three to six months.

Iron in many forms was used. Oral administration is preferable. Organic iron is expensive. Adequate doses are requisite; these vary with individual needs. "Double barreled" therapy (for example, vitamin, iron, liver and copper combinations) has a place but only "in the face of a demonstrated multiple deficiency, or of failure to work out the actual state of affairs" (Davis (26)).

Our experience is identical. In this study iron was given in many forms. By a process of elimination, ferrous sulphate came to be the product of choice. After a preliminary and protracted use, Blaud's pills were discontinued because of relative unabsorbability; tincture of iron chloride because of gastric irritation; iron and ammonium citrate and reduced iron because of gastric discomfort and diarrhoea. All of these products, if given adequately, call for larger doses than ferrous sulphate and have a slower therapeutic effect.

In addition to the various clinical and laboratory indications for the treatment of anaemia, persistent or early microcytosis should not be overlooked. Very recently, Guest and Brown (27) have expressed similar belief. In a few patients large doses of reduced iron were suspected of causing menorrhagia and relief from this complaint occurred with the discontinuation of iron. Except in the cases of menorrhagia

it was found that contraindications to the use of iron are few. Patients who have constipation, which increases with the use of iron, should have an appropriate cathartic. Constipation should be avoided particularly in the positive sputum cases and those subject to haemoptysis. If the inferred theory as to the aetiology of intestinal tuberculosis has any significance, then increasing constipation in the presence of a positive sputum tends to favor the implantation of tubercle bacilli. Lastly, increased constipation and strain during a period of haemoptysis and for some time thereafter is to be avoided as far as possible with catharsis and a mild form of iron.

It should not be surprising in a disease like pulmonary tuberculosis that functional gastric disturbances are present or are aggravated by irritating medication, particularly in the far advanced patient in whom the incidence of intestinal tuberculosis is great. During the last two years of this study specially coated tablets of ferrous sulphate[3] were used. Fifty-four patients were included in this observation. The dose varied from 9 to 12 grains daily and occasionally 18 grains. Each tablet of 3 grains of ferrous sulphate is equivalent to about 20 grains of iron and ammonium citrate. From this study it is concluded that (*1*) ferrous sulphate stimulates erythropoiesis, (*2*) causes an increase in size of the red cells and (*3*) leads to a more rapid increase in haemoglobin without gastrointestinal upset than when ferric or simple reduced iron are given in adequate doses. Prolonged administration of this drug for a year in some patients was without untoward effects. The same may be concluded for any easily absorbed ferrous salt.

The maintainance dose of each form of iron is a variable one because of individual needs. Briefly, the deciding factors are: age, sex, the initial red cell count and haemoglobin level, chronicity and severity of the pulmonary lesion and complicating disease. In cases of diarrhoea the doses were necessarily greater and ferrous sulphate is preferred. After a few months of iron administration by mouth, the body apparently builds up a reserve of this metal. On the average this is depleted in two or three months after its discontinuation and if the cause of the anaemia persists. Patients scheduled for thoracoplasty were often prepared by daily doses of iron six to eight weeks in advance of their operation. Iron was often continued during the periods between stages. Haemoglobin stores are either moderately or markedly reduced following every stage of thoracoplasty.

[3] Feosol.

Other forms of therapy have been proposed for the treatment of anaemia of the tuberculous. Codliver oil and tomato juice have no direct effect on anaemia. Their main value lies in the treatment of malnutrition and of intestinal tuberculosis. The same can be said of artificial heliotherapy, stomachics and tonics. All act indirectly by improving the patient's well-being and increase the desire for food. Whipple (28), working on the production of haemoglobin in anaemic dogs on various diets, found that fish liver and codliver oil were inert and that fish as a class stands with bread and milk. The latter foods have a minimal influence on haemoglobin regeneration in dogs. Experiments with anaemic albino rats, which were fed codliver oil without iron and copper, continued to show declining haemoglobin values (29). And here again it may be stated with advantage that even though the appetite and the assimilation are good, and the dietary correct, the anaemia may persist because of the nature of or hindrance from the pulmonary lesion or possible complications. Food iron must be supplemented by adequate amounts of prescribed iron.

Not one of the 137 patients in this study who received iron needed copper. Hypercupraemia has been found in the tuberculous patient (30). There is a sufficient amount of this metal in an adequate diet. Bence and his associates (31) determined that "the copper content of the blood of anaemic patients is increased whenever the functional activity of the bone marrow is intensified, regardless of whether the existing disorder is pernicious anaemia, secondary anaemia, leukemia or polyglobulism."

If the therapeutic response to iron is either slow or absent one should suspect (*1*) intestinal tuberculosis, (*2*) smouldering activity of the pulmonary lesion, (*3*) any one of the many complications—pleuritis, amyloid, bleeding haemorrhoids, unreported haemoptyses or anorexia resulting in an inadequate dietary intake and (*4*) the patient's failure to take faithfully the prescribed iron.

The use of liver extract in this study has not been tried sufficiently to warrant any general conclusion. An occasional patient with amyloid who showed moderately good results from iron experienced further improvement from the parenteral administration of primary liver extract. Liver extract may in a limited way supply a need for "something." Seddon (32) has reported on the beneficial but not curative results with the parenteral use of liver extract in amyloid disease. In our limited experience with far advanced patients, daily intramuscular injections

of a primary liver extract (and in one instance for three months) did not seem to affect the patient considerably. It has been claimed that amyloidosis will disappear after adequate surgical drainage and treatment of its cause (31, 33, 34, 35).

The degree of the pulmonary lesion and its complications determine the therapeutic response to iron. The difficulties mount as the activity of the lesion increases in its severity and chronicity. A group of 48 patients was divided into active and nonactive cases. In the febrile group the therapeutic response to iron was definitely less than in the afebrile group. Furthermore, the patients who received iron and ammonium citrate did better than those who received uncrushed Blaud's pills irrespective of activity or stage of disease. Both groups received adequate doses. The desired haematopoietic response was greater and much faster in the iron-treated group than in the group who received no iron.

Parenteral administration of iron is costly and laborious. Adequate doses of iron, whether given intramuscularly or intravenously, are often too near the toxic dose to warrant its frequent use. This is true particularly of the intravenous preparations (36, 37, 38).

Discussion has centred around the relative therapeutic value of ferrous and ferric iron salts. Theoretically, when equivalent therapeutic doses of the various forms of iron are administered, there should be the same haematopoietic response provided there is sufficient gastric acidity and all other things are equal. Recently Gray and Melnick (39) demonstrated hypochlorhydria or anacidity in pulmonary tuberculosis. They and others found that hypoacidity and anacidity in all stages of pulmonary tuberculosis vary from 33 to 50 per cent. Mettier and Minot (40) believed haematopoiesis is somewhat dependent upon the acidity of the gastrointestinal tract. They did not imply that iron must be given in an acid medium, for apparently, if a sufficient dose is given in an alkaline medium, suitable responses of the bone marrow will ensue. Furthermore, these authors maintained that "in order to obtain an optimum effect, a larger amount of the iron salt must be given when the duodenal contents are alkaline than when they are acid." In this study varying responses to iron were noted. Better results were obtained in some than in others with comparable pulmonary disease. Unfortunately it was not possible to carry out a correlative study with iron therapy in pulmonary tuberculosis between anaemia and gastric function.

Many observers indicated their preference for ferrous iron salts and obtained better responses than with ferric iron (41, 26). Witts (36)

stated that "in addition to the physiological states which increase the requirements for iron there are pathologic conditions which impair their absorption and give rise to a 'conditioned deficiency.' The most important is achlorhydria. Hydrochloric acid is not necessary for the absorption of iron if adequate amounts of the latter are present." In the presence of an adequate amount of iron some of the ferric ions are reduced to the ferrous state and absorbed in this latter form. But, if iron is prescribed in the ferrous state, large doses are not necessary, and therefore this fact probably explains the better results from smaller doses of ferrous chloride, ferrous carbonate and ferrous sulphate. Witts has further stated that "the optimum dose of reduced iron and of iron and ammonium citrate is higher in patients with achlorhydria than in those with normal gastric secretions."

Brock and Diamond (42) and Deabold and Elvehjem (43) reported on the dangers of prolonged administration of iron. Their objections are based on studies on children or young experimental animals. Brock and Diamond came to their conclusion by inference from the dangers of producing rickets in children who are receiving iron and who are or may be on a diet low in phosphorus. Experimentally they found the addition of ferric chloride to a nonrachitogenic diet caused the appearance of rickets in white rats. Increase in phosphorus content of the diet prevented the production of rickets in the animals on the ferric chloride diet. These authors assumed that iron enters into a chemical combination with the phosphorus in the intestinal tract to form compounds which are relatively difficult to absorb and that phosphorus depletion results. The opinion was the same about other compounds of iron which also produced rachitic changes in rats when given with a normal diet. They concluded that the continual and prolonged use of large doses of iron in a child on a diet somewhat low in phosphorus might lead to the same result as a diet low in phosphorus alone. The group of patients who are the basis of this study are all adults (with a rare exception) and therefore out of danger in the development of rickets. Osteomalacia, which was not encountered in this study, should not appear in adults if the diet contains adequate amounts of calcium, phosphorus and vitamin D.

Menkin (44), after repeated intravenous injections of ferric chloride into rabbits, concluded that (*1*) it accumulates in tuberculous areas and (*2*) that the course of the disease is retarded. More recently, Steinmann (45), from observations on iron storage in tuberculous tissue,

concluded that iron collects, not in the actual tuberculous focus, but in the tissues immediately adjacent thereto, and that the animals with and the animals without iron therapy fare equally well.

It cannot yet be stated statistically that the patients who received iron therapy now have a better prognosis than those who did not. No literature avails to justify conclusions in this respect. Clinically, the iron-treated group fared better symptomatically than the other group. It is obviously impossible just now to make clinical evaluation on a prognostic basis short of several years.

SUMMARY

The anaemia associated with pulmonary tuberculosis was studied in 509 patients. The venous method of obtaining the blood was preferred. Bone marrow sections were obtained from about 100 patients at thoracoplasty and at autopsy.

As the amount and chronicity of the pulmonary disease increases, the number, size and haemoglobin content of the red cells decrease. A consideration of these factors alone does not completely reveal the incidence of anaemia. Its incidence increases to 46.0 per cent when the mean corpuscular haemoglobin concentration is also taken into account. The most common types of anaemia encountered are hypochromia and microcytosis.

In the routine care of most tuberculous patients, the correction of the sedimentation rate of the red cells for anaemia is not necessary unless the anaemia is severe.

The icterus index values drop, often close to two units, as the amount and severity of the pulmonary lesion increase. It is believed there is a partial inhibition of haemoglobin synthesis with an increasing severity of the pulmonary tuberculosis.

In the treatment of the anaemia associated with pulmonary tuberculosis, ferrous salts are the most effective. It cannot yet be stated statistically that the patients who received iron therapy now have a better prognosis that those who did not. Clinically, the iron-treated group fared better symptomatically than the other group.

The author is very grateful to the following whose kindness and assistance made this study possible: Drs. S. H. Remick, H. F. Newton, R. Z. Schulz, A. Branch, B. H. Douglas, E. J. O'Brien, H. S. Willis, C. E. Woodruff, J. Kasper, W. B. Castle, H. Evarts, and Misses O. F. Allebaugh, E. Marsh, M. Dingle and E. Chase, and the resident medical staff and patients of both hospitals.

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NORMAL SEDIMENTATION RATE IN OPEN PULMONARY TUBERCULOSIS[1]

ANDREW L. BANYAI AND ESTHER CALDWELL

In 1930 one of us (1) published a communication on the erythrocyte sedimentation test in 2,000 cases. Of these, 1,741 were found to be tuberculous, the balance had diseases other than tuberculosis. At that time it was found that 128 patients, or 7.35 per cent of those who showed evidence of an active tuberculosis, had a normal sedimentation rate by the Westergren method. Of these 128 patients, 81 had pulmonary tuberculosis with a frank parenchymal infiltration; there were 19 with tuberculosis of the hilar lymph nodes, 6 with tuberculous pleurisy, 1 with tuberculous peritonitis, 13 with orthopedic forms of tuberculosis, and 8 with tuberculous cervical lymphadenitis. Of the 81 patients with pulmonary tuberculosis who had a normal sedimentation rate, positive sputum was found in 34. This finding brought to light the important fact that normal sedimentation velocity and positive sputum may coëxist. Consequently, attention was called to the fact that, because such a possibility detracts from the reliability of the sedimentation test in diagnostic work, it should serve as a warning against the enthusiasm of those who consider a normal rate as evidence of the absence of active tuberculosis; a method with such working error should not be considered equal in value to the demonstration of tubercle bacilli in the sputum, or a trustworthy criterion for ruling out tuberculosis, unless all other information—clinical, roentgenographic and laboratory—is corroborative.

During the past eight years 5,274 patients were admitted to Muirdale Sanatorium with pulmonary tuberculosis. Of these, 489 had minimal, 2,007 moderately advanced, and 2,778 far advanced tuberculosis according to the classification of the National Tuberculosis Association. Normal sedimentation rate and positive sputum were found in 111. The coëxistence of these two findings was recorded on admission to the institution in 74 and during sanatorium stay in 37. There were only

[1] From Muirdale Sanatorium, Wauwatosa, Wisconsin, and the Department of Medicine, Marquette University Medical School, Milwaukee, Wisconsin.

two colored patients in this group. There were 89 men and 22 women. Seven were under 20 years of age, 48 between 20 and 29, 31 between 30 and 39, 15 between 40 and 49, and 10 over 50 years of age. Six cases were classified as minimal, 85 as moderately advanced, and 20 as far advanced. The following complications were observed: tuberculous laryngitis in 7, silicosis in 5, bronchiectasis in 2, tuberculous epididymitis in 2, and one of each of the following conditions: chronic cholecystitis, tuberculous lymphadenitis, diabetes, postpoliomyelitic paralysis, pleuropericardial adhesions, latent syphilis, and mitral insufficiency.

The distribution of localizing and constitutional symptoms was as follows: cough in 90 (81 per cent), expectoration in 94 (84.6 per cent), pulmonary haemorrhage in 11 (9.9 per cent), thoracic pain in 52 (46.9 per cent), dyspnoea in 38 (34.2 per cent), chills in 11 (9.9 per cent), fever in 5 (4.5 per cent), night sweats in 19 (17.1 per cent), loss of appetite in 21 (19.8 per cent), loss of weight in 52 (46.9 per cent), malaise in 39 (35.1 per cent), and a pulse rate of 90 or more in 72 (64.8 per cent). On physical examination moist râles over the lungs were not detected in 13 (11.7 per cent). Moist râles were heard over one-half of one lung in 49 (44.1 per cent), over an area corresponding to the extent of one lung in 36 (32.4 per cent), and over an area larger than the extent of one lung in 13 (11.7 per cent). No simultaneous roentgenograms were available in 25; in the remaining 86 the roentgenological findings were as follows: the lesion was of the exudative type in 9, fibrocaseous in 57, fibrotic in 17, predominantly calcifying in character in 2, and the roentgenogram showed no demonstrable lesion in 1. The latter patient, R. K., 32 years old, a white man, was admitted to Muirdale Sanatorium with a minimal pulmonary tuberculosis on September 27, 1934. At the time of admission he complained of cough, expectoration, haemoptysis, thoracic pain and dyspnoea, also of malaise, chills, night sweats, loss of appetite and loss of 20 pounds in weight. Beside the positive sputum, he showed a marked tuberculin reaction, 30 to 40 mm. in diameter, with considerable swelling, to a 1:100,000 dilution of OT. The monocyte-lymphocyte ratio was normal. One of the patients with a predominantly calcified lesion was A. K., a white woman, aged 35 years, admitted with a moderately advanced pulmonary tuberculosis on January 29, 1934. At that time she complained of chills and thoracic pain. Moist râles were present over the upper one-third of the right lung. She had a two-plus tuberculin reaction to 1:100,000 dilution. The monocyte-lymphocyte

ratio was 0.4. The other patient with a similar type of lesion, G. R., a white male, aged 27 years, had a tuberculous involvement of both upper lobes. His complaints were cough, expectoration, thoracic pains, dyspnoea, loss of weight and malaise. The tuberculin reaction was positive only to the 1:1,000 dilution. The monocyte-lymphocyte ratio was 0.4.

In our previous publication on the sedimentation test (1) we reported that out of 54 moderately advanced cases with normal sedimentation speed a single cavity was demonstrable in 7 and multiple cavities in 1; of 13 far advanced cases with normal sedimentation velocity multiple cavitations were found in 2 and a single cavity in 2. In the present series small cavity, including honeycombing, was reported by the roentgenologist in 8 (7.2 per cent), moderate sized cavities were found on the roentgenogram in 14 (12.6 per cent), and a large cavity was found in 1. The fact that normal sedimentation rate may occur in the presence of a cavity contributes additional weight to our impression that the use of the sedimentation test for the exclusion of active pulmonary tuberculosis has considerable limitations.

A study of the simultaneously taken monocyte-lymphocyte ratio in 87 cases showed that it was 0.4 or less in 46, between 0.4 and 1 in 38, and more than 1 in 3. The tuberculin test (Mantoux) was positive to the 1:100,000 dilution in 102 cases. The intensity of the tuberculin reaction was recorded as follows: it was 100 square millimetres or less in 18; between 100 and 400 square millimetres in 57; 400 to 600 square millimetres in 7; 600 to 900 square millimetres in 10; and more than 900 square millimetres in 10. The remaining cases showed a positive reaction to stronger dilutions of OT or to PPD. It might be of interest to quote Schilling (2), who pointed out that marked degree of allergy to tuberculin may cause a slowing down rather than an increase in the rapidity of sedimentation.

Berg (3), analyzing the records of 2,422 cases, reported that there were 18 patients in this group who had positive sputum and normal sedimentation rate. Sopp (4) found that 6.6 per cent of his dispensary patients had open pulmonary tuberculosis and normal sedimentation rates. The coëxistence of progressively increasing cavitation and normal sedimentation rate was described by Breuhaus (5) in seven instances. Tillisch (6) reported on 19 patients who had positive sputum and normal sedimentation rate at the same time.

SUMMARY AND CONCLUSIONS

A study of the relationship between positive sputum and the sedimentation test in 5,274 cases of pulmonary tuberculosis is reported. It was found that in 2.1 per cent of these patients normal sedimentation rate and positive sputum were present at the same time. The symptomatology and simultaneous roentgenological findings corroborated the presence of an active parenchymal pulmonary tuberculosis in the great majority of instances.

The analysis of our clinical material revealed not only the possible coëxistence of an active pulmonary tuberculosis and normal sedimentation velocity but also that single or multiple cavities may coëxist with a normal sedimentation rate.

The most plausible explanation of the varying rates of the sedimentation of the red blood cells is a disturbance of the colloidal balance of the blood. As a rule, there is a parallelism between the activity of the tuberculous process and the colloidal balance of the blood. Consequently, tissue destruction or tuberculous toxaemia that upsets the equilibrium of the serum proteins is usually recognizable by an increased sedimentation speed.

The exceptions to this rule, as found by us and by others, can be explained by the hypothesis that there are certain cases of pulmonary tuberculosis in which the colloidal balance may remain normal during the active stage of the disease, or it may return to normal prior to the cessation of activity of the tuberculous process.

We are of the opinion that, although these exceptions do not invalidate the value of the sedimentation test, its limitations should be recognized and, therefore, a normal sedimentation rate should not be considered an infallible evidence of the absence of an active pulmonary tuberculosis.

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ERYTHROCYTE SEDIMENTATION

Its Practical Value in an Ambulatory Tuberculosis Clinic

HARRY T. PESSAR[1] AND ALLAN HURST[2]

Numbers of papers and reports on the value of the erythrocyte sedimentation rate as a test of activity in pulmonary tuberculosis have appeared in the literature since Fahraeus first published his observations in 1918.

The most interesting feature of these reports is the prevailing tendency on the part of the different writers to regard the test (*1*) as a useful and practical method for obtaining accurate and dependable information about the actual progress or retrogression of a tuberculous lesion, and (*2*) as a sensitive indicator of favorable or unfavorable changes in a tuberculous individual, before these can be demonstrated by other clinical and laboratory procedures.

Most of the writers on the subject are inclined to see a definite correlation between the sedimentation rate of the red blood cells and the state of activity in the tuberculous lesion. Changes in the sedimentation rate, according to these authors, exactly parallel alterations in the tuberculous focus. A decided tendency in the sedimentation rate toward the normal shows a tendency in the tuberculous process toward arrest and healing, while a persistently high sedimentation rate is the foreboding of an active and relentlessly progressive disease.

The Mott Haven Tuberculosis Clinic is an independent field unit completely detached from hospital or sanatorium connections. It constitutes an important link in the chain of tuberculosis clinics by means of which New York City exercises its administrative control and medical supervision of the tuberculous in a community of approximately 225,000 population. Because of limited clinic facilities and limited budgetary appropriations it becomes necessary that services be limited to the most suitable cases.

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It is not to be wondered at that in our search for a possible solution to the disturbing problem of selection, we were impressed by the enthusiastic reports concerning the diagnostic and prognostic value of the sedimentation test.

In order to determine the precise value of the erythrocyte sedimentation test as an indication of activity in a tuberculous patient, and the extent to which it can be relied upon in the selection of cases suitable for dismissal from clinic supervision and for discontinuation of treatment, we inaugurated in February, 1936, the following study in the diagnostic and pneumothorax services of the Mott Haven Health Center of the New York City Department of Health.

MATERIAL FOR THE STUDY

The material selected for the study included the following groups of patients from the diagnostic and pneumothorax clinics:

1: All adult suspects who were found to be free from clinical tuberculosis, and after a short period of observation were finally diagnosed as not having active tuberculosis. This group was used as a control.
2: All patients who, after a period of observation and study by means of physical examinations, serial X-rays and laboratory findings, were finally classified as "arrested cases."
3: All recently diagnosed cases of clinical tuberculosis awaiting admission to an institution.
4: All ambulatory patients receiving pneumothorax refills in the pneumothorax clinic.
5: All patients in whom collapse therapy was voluntarily or involuntarily terminated following a shorter or longer period of observation in the pneumothorax clinic.

For the test we used a modification of the Westergren distance method. In this test the distance is measured through which red cells have sedimented in a tube calibrated in 40 mm. (the Thompson tube) at the end of one hour. The distance in millimetres is recorded as the sedimentation index. Although we made no correction for anaemia, we found the test sufficiently accurate for the purpose of the study.

METHOD OF STUDY

On patients visiting the diagnostic and follow-up clinic the sedimentation test was done. An effort was made to repeat all tests on diagnostic cases at least once, but this was not always feasible. Diagnosis and

prognosis were judged by the usual clinical standards, that is, pulse, temperature and respiration, physical examination, X-ray and sputum findings. Where there was any doubt as to the exact status of a patient, serial X-ray examinations were made at frequent intervals.

Patients with upper respiratory infections and other obvious infections, observed on routine examination, were ruled out of the study. In female patients menstruation and pregnancy were considered to vitiate the accuracy of the test. Such patients were also excluded from the study. Because of the nature of our clinic facilities, gynecological examination was not available. Latent abnormal pelvic conditions

TABLE 1

Results of sedimentation tests performed in the diagnostic clinic on 188 nontuberculous contacts, 143 arrested cases, and 167 active progressive cases

SEX	TOTAL NUMBER OF PATIENTS	TOTAL NUMBER OF TESTS	SEDIMENTATION		VARIATION FROM EXPECTED RATES	
			Range	Average rate	Number	Per cent
Nontuberculous contacts (188)						
Male	69	79	2–24	7.2	11	15.9
Female	119	150	2–27	11.2	34	28.5
Arrested cases of tuberculosis (143)						
Male	78	148	2–25	8.4	13	16.6
Female	65	136	3–24	11.4	17	26.1
Cases of active progressive tuberculosis (167)						
Male	90	174	2–28	19.6	12	13.3
Female	77	141	6–38	19.2	14	18.1

could not therefore be absolutely ruled out, although we were fully aware of the influence of such conditions.

We have used the normal values set up by other investigators. Sedimentation rates of 10 mm. for males and 12 mm. for fremales have usually been accepted as high normals. In this paper we have taken 12 mm. for males, and 14 mm. for females as high normals in order to allow for any possible variation in technique, anaemia or temperature of the working room.

Table 1 shows the results in 188 contacts without pulmonary tuberculosis, 143 cases of arrested tuberculosis, and 167 individuals with active progressive tuberculosis in the diagnostic clinic.

It will be noted from table 1 that in the contact, apparently normal nontuberculous cases over 28 per cent of the female patients and approximately 16 per cent of the male patients studied showed sedimentation rates above an accepted high normal standard. The greater percentage of variations in the females can possibly be explained on the bases of existing latent abnormal gynecological conditions which we could not definitely rule out because of a lack of facilities for pelvic examinations.

Similarly, in the group of cases of arrested tuberculosis we found impressive variations from an expected standard. These variations amounted to more than 26 per cent in the female group, and 16.6 per cent in the male patients.

In the cases of active tuberculosis also marked variations were found. In this group more than 18 per cent of the females and 13 per cent of the males gave figures below those expected for progressive, active cases.

A somewhat different procedure was carried out with the pneumothorax group. All patients who come to the clinic for the continuation of pneumothorax have been treated previously in some hospital or sanatorium for a period ranging from nine months to one year. Generally their sputum has been negative for about six months. They are usually in good general health having had the benefit of good care and supervision. Decisions as to changes in therapy do not have to be made immediately in most instances, and attention therefore is not focused on the individual sedimentation rates. Frequently it was surprising to find a high rate in an apparently favorable case, but no conclusions were drawn until we had had an opportunity to observe the patient for a considerable period, and to do repeated sedimentation tests. It is possible therefore to discuss the general trend of the sedimentation rates in this group, rather than averages and variations.

Since 1932 we have treated in our clinic 131 patients with pneumothorax. In this we include only living patients with follow-up records to date. We have excluded all patients who have died, those who have been readmitted to hospitals without returning to us, or those with active rheumatic heart disease.

Because of the varying length of time of pneumothorax, with or without complications, and because of a large number of patients with reexpanded lungs, it was thought best to divide them into two main groups, namely, favorable and unfavorable cases. As will be observed in tables 2 and 3, the favorable cases were further subdivided to show the period of collapse, number of voluntary reëxpansions and involuntary

reëxpansions because of obliterative pleuritis. Small effusions in the costophrenic sinus were not considered unfavorable, since they in no way interfered with the treatment, and they occurred in the majority of cases. The unfavorable cases were subdivided into four groups, namely, those with empyema, active contralateral disease, ineffective pneumothorax, and large serous effusions. While the last mentioned effusions may not always be of poor prognostic influence, it was felt that anything interfering with the continuation of collapse should be included among the unfavorable cases.

TABLE 2

Trend of the sedimentation rates in 101 favorable pneumothorax cases

PERIOD OF OBSERVATION		CONSISTENTLY HIGH	DOWN TO NORMAL	NORMAL TO HIGH	REMAINED NORMAL
One year	11	7	0	1	3
Two years	22	7	1	3	11
Three years	16	9	1	4	2
Reëxpansions:					
Voluntary	47	7	9	8	23
Involuntary	5	0	2	0	3
Total	101	30	13	16	42

TABLE 3

Trend of the sedimentation rates in 30 unfavorable pneumothorax cases

COMPLICATIONS	CONSISTENTLY HIGH	ABOVE NORMAL	NORMAL
Empyema	1	0	5
Active contralateral disease	6	2	0
Ineffective pneumothorax	5	3	0
Large clear effusion	5	2	1
Total	17	7	6

Among the favorable cases, there were 30 patients whose sedimentation rates remained consistently high. If it were contended that 7, or 23 per cent, of these cases fell within the one year group, and thus had not been observed for a sufficient period to have attained a normal sedimentation rate, there still remained 23 in the high group, 7 of which continued high into the two year group, 9 in the three year group, and 7 reëxpanded cases with collapse of at least three years' duration. This is a variation of 22.8 per cent among 18 females and 5 males.

Among the unfavorable cases, 4 males and 1 female with empyema showed normal sedimentation rates, as well as one patient with a large serous effusion giving a deviation of 20 per cent.

DISCUSSION AND SUMMARY

In a recent article Bannick, Gregg and Guernesey (1) discussed the relative importance of the various techniques employed in performing the erythrocyte sedimentation test with special reference to the type of tube used. They compare the degree of accuracy in the results shown when the Cutler (50 mm.) tube is used with that of the Wintrobe (100 mm.) and the Westergren (200 mm.) tubes. These authors point out that because of its greater length, and consequent lesser tendency to packing of cells, the Westergren (200 mm.) tube gives the most accurate results. In our study we used the Thompson tube which is calibrated to 40 mm. It is practically the same as the Cutler tube. The Thompson tube was used because it was immediately available. In comparative studies it has been found that for the first 18 to 20 mm. the speed of sedimentation is approximately the same, no matter what type of tube is used. Beyond 20 mm., packing begins to show itself in the shorter tube. Since a rate of 18 mm. per hour is well above the accepted standard for normal individuals, we feel that for general work the Cutler and Thompsons tubes give values which are adequate for most practical purposes.

Judged by the reports of many investigators, there appears to be ground for the belief that an average standard sedimentation rate can be established for normal persons, and that in tuberculous individuals with active disease, this normal standard is invariably exceeded. The degree of increase in the rate is considered to be an expression of the degree of activity in the tuberculous focus. Furthermore, a continued reduction in the sedimentation rate with a persistent tendency to approach the normal standard reflects an unmistakable tendency of the lesion to retrogression and healing.

So far as could be determined by us there has been no study made of the results which follow upon the practical application of the above concepts in an ambulatory clinic. The purpose of our study has been to determine whether the sedimentation reaction could be utilized in a practical way to screen out, of the thousands of individuals who are supervised in our clinic, those who may not be in need of such supervision.

Analyzing the facts brought out by our study, we are forced to the

conclusion that the sedimentation test offers no answer to our problem of selection. Of 229 negative contacts tested, we found sedimentation rates above a generally accepted normal in 28 per cent of the females, and 16 per cent of the males. Of 143 arrested cases observed in the course of our study, similarly important variations were found: in 26 per cent of the female patients and 16 per cent of the males, the sedimentation rate did not parallel the improvement shown by serial X-ray studies, and a favorable clinical course as evidenced by a return of pulse, temperature and respiration to normal, a gain in weight, loss of cough, lessened expectoration, disappearance of bacilli from sputum, etc. Of 167 cases with active tuberculosis, more than 18 per cent of the females and 12 per cent of the males gave values below those expected for active cases.

We made no attempt to separate the various pathological types of tuberculous lesions. It is a well established fact that perifocal reactions and exudative processes cause a change in the clinical and X-ray pictures of the patient, and in the majority of instances these changes are accompanied by a rise in the sedimentation rate. However, when the exudative reaction clears and the end-stage process with cavity formation remains, the sedimentation rate shows a gradual reduction, giving rise to unfounded optimism and a false sense of security.

In a study of 152 patients with pneumothorax, with and without complications, we observed 30 patients in whom the sedimentation remained consistently high over a period varying from one to three years in the face of clinical and X-ray evidence of an arrested or healed lesion. In a group of patients with ineffective collapse or grave complications, the sedimentation rate remained normal, thus giving not the slightest warning of the serious nature of such conditions in 6 out of 30 cases, thus leading to error in 20 per cent of the group.

The facts brought out by our study have served to arouse in us a profound skepticism concerning some of the most important claims in favor of the sedimentation test, namely, that progressive changes in a tuberculous lesion are constantly reflected in an increased sedimentation rate, and that a reduction in the sedimentation rate shows a retrogression of the pathological process. Quite a few of our clinically active cases, which radiographically had been shown to have cavernous caseous pneumonic phthisis, were found to have an average normal sedimentation rate.

As for the significance of the sedimentation test in prognosis, it seems

to us that the very protean nature of the disease precludes the possibility of making correct predictions as to end results in the individual case. The answer to the problem of prognosis is certainly not to be found in any single line of investigation. All available fact-finding methods in clinical investigation must be utilized as a basis for intelligent prognosis.

We realize fully that our series is not large, and that the period of observation might have been too short in some of the arrested cases with high sedimentation rates to warrant a final conclusion as to the value of the sedimentation test in pulmonary tuberculosis. We do feel, however, that the facts revealed thus far in our study are sufficient to cast serious doubt on some of the claims made in the literature. It is hoped that the report of our findings will stimulate further study of the problem by other investigators which will result in a more correct evaluation of the sedimentation test in the diagnosis and prognosis of pulmonary tuberculosis.

The authors desire to express to Dr. Herbert R. Edwards, Director of the Bureau of Tuberculosis, their appreciation for his helpful criticism and suggestions for the improvement of the text, and also to Miss H. Connell and Miss T. Tomaselle of the clerical staff for their help in setting up the tables and preparing the manuscript.

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CULTURE OF TUBERCLE BACILLI[1]

1. The Effect of Sodium Hydroxide and Sulphuric Acid upon Acid-Fast Variants of Homologous Strains and the Influence of the Hydrogen Ion Concentration in Different Media upon Subsequent Growth

W. STEENKEN, JR. AND M. M. SMITH

Many authors have championed different media for the isolation and culture of tubercle bacilli and other acid-fast microörganisms from human and experimental lesions. Various methods of digestion have been proposed to rid the exudates of contaminating bacteria, the most important of which involve the use of either sulphuric acid or sodium hydroxide.

Recent reports have raised a question as to whether each of these different media is equally effective with either method of digestion and whether the type of microörganisms which grow will always be the same regardless of the preliminary treatment. From human urine and sputum Pinner (1) has isolated atypical acid-fast microörganisms which, in the first generation, were nonpathogenic for laboratory animals, but which later became virulent for guinea pigs after serial passage. In two specimens of human spinal fluid and two sputa and pus from a tubercle bacillus abscess, Smithburn (2) has demonstrated the presence of both rough and smooth colonies of tubercle bacilli. He has suggested that preliminary treatment with sodium hydroxide or sulphuric acid may have altered the microörganisms, thereby changing the relation on culture of S to R colonies. Not having an S variant of the human type tubercle bacilli, we were unable to include one in this study.

To shed more light upon some of these questions the stabilized variants of a number of thoroughly investigated strains of acid-fast bacilli from human sources were each subjected to the following treatment: aliquot portions of homogeneous suspensions of various cultures were treated with sulphuric acid and with sodium hydroxide in the manner recommended for digestion. A standard quantity of the treated suspension was planted upon tubes of five standard culture media (3, 4, 5, 6, 7). The reaction of the media was adjusted at two levels in each case, one acid at pH 6.2 and the other alkaline pH 7.2.

[1] From the Research and Clinical Laboratory, Trudeau Sanatorium, Trudeau, New York.

The four strains of acid-fast microörganisms used for the tests were as follows:

1: I.P. A nonpathogen isolated from sputum by Dr. E. R. Baldwin and dissociated into I.P. (I and II) by Steenken and Landau (8).
2: M. A nonpathogen strain isolated from sputum by Professor Lyle Cummins and Williams, and dissociated into M (I and II) by Steenken and Landau (8).

TABLE I

CONSTITUENTS	PETRAGNANI	PETROFF	HOHN	LOEWENSTEIN	CORPER
KH_2PO_4			0.812 gm.		
K_2HPO_4				0.41379 gm.	
Na_2HPO_4			0.608 gm.		
Na Citrate				0.41379 gm.	
Mg Citrate			0.507 gm.		
$MgSO_4$			0.122 gm.	0.41379 gm.	
Asparagin			1.217 gm.	1.24137 gm.	
Alanin			0.812 gm.		
Peptone	2.24 gm.				
Glycerin	26.10 cc.	50.00 cc.	24.30 cc.	59.92 cc.	26.7 cc.
Skim milk	335.80 cc.				
Potato flour	13.43 gm.			17.543 gm.	
Whole potato	223.90 cc.				
Egg	358.20 cc.	631.11 cc.	750.00 cc.	467.82 cc.	
Egg yolk	33.60 cc.			43.85 cc.	668.1 cc.
Beef Infusion		Double strength 315.56 cc.			
H_2O			203.00 cc.	413.79 cc.	275.60 cc.
Dye	2% malachite-green 22.40 cc.	1% alcoholic gentian-violet 3.33 cc.	0.7% malachite-green 22.7 cc.	5% Congo red 14.62 cc.	1% Congo red 29.60 cc.
pH before inspissation	6.40	7.00	6.90	6.90	6.30
pH after inspissation	6.65	7.26	7.14	7.14	6.53

3: H37. A virulent strain isolated from sputum in 1905 by Dr. E. R. Baldwin and dissociated by Steenken, Oatway and Petroff (9).
4: R1. A strain originally virulent, isolated from the lung of a child dying of miliary tuberculosis by Dr. E. L. Trudeau (1891) (10).

Acid and alkali digests of both variants of each strain were planted upon media whose reaction had been adjusted to acid and to alkaline reactions. The chemical composition of the different media is shown in table I.

EXPERIMENTAL PROCEDURES

As indicated in table I the process of inspissation increases the final pH of the different media by approximately 0.2. It is therefore necessary to adjust them this much lower before inspissation. Each batch of media was accordingly divided into two parts and adjusted to a pH of 6.0 and 7.0 respectively. They were then inspissated on two successive days for one and a half hours at 80°C. A final check on the reaction was made by cutting out a small cube of medium from one tube in each batch and testing its pH with a Cullen & Biilmann quinhydrone electrode and a L & N potentiometer (11). Final pH was 6.2 and 7.2 respectively.

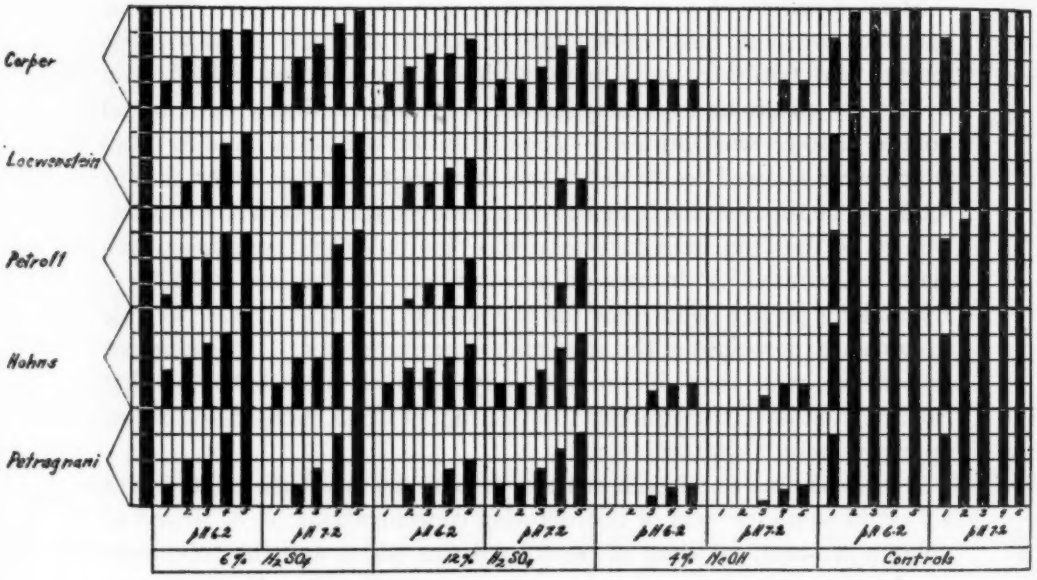
Standardization of dose: From sixteen day old cultures on Proskaur and Beck synthetic medium, one loop of pellicle was removed to a sterile mortar and triturated with physiological saline solution, added drop by drop to ensure an even suspension. This was continued until a final volume of 10 cc. was obtained. The suspension was transferred to tubes which were allowed to stand for ten minutes to let the larger clumps settle. The supernatant fluid was then removed with a capillary pipette. One cc. of the fluid from each tube was pipetted into a weighed watch glass, evaporated to dryness on a water-bath, cooled and reweighed. By making proper deductions for the sodium chloride, it was possible to calculate the weight of the dried microörganisms per cc. The different suspensions were then diluted with physiological salt solution so that each cc. contained the equivalent of 0.1 mg. of dried microörganisms, or approximately 30,000,000 bacilli.

Digestion: One cc. of each of these suspensions was then treated with 4.0 cc. of sulphuric acid of the following concentrations: 6, 8, 10 and 12 volume per cent. A drop of phenol red was added and the tubes were incubated, both at room temperature and at 37.5°C. Another series of suspensions was similarly treated with 1.0 cc. of 4 per cent sodium hydroxide and likewise incubated at room temperature and at 37.5°C. All suspensions were left in contact with the digestion mixture for thirty minutes. At the end of this time, they were centrifuged at high speed for ten minutes, the supernatant fluid decanted and the remaining sediment neutralized either with N/10 sodium hydroxide or with N/10 hydrochloric acid. The tubes were then filled with sterile saline, and again centrifuged at high speed for ten minutes and the supernatant fluid decanted. Sufficient sterile saline was added to the remaining sediment to bring the volume up to the original volume of 10 cc. After thorough shaking, one loopful of each digested suspension was then streaked on the surface of a slant of each of the various media. During

a five week period of incubations at 37.5°C., weekly measurements of the growth were recorded. In the following charts, we have indicated the amount of growth after digestion with 6 and 12 per cent sulphuric acid and after 4 per cent sodium hydroxide; the effect of 8 and 10 per cent sulphuric acid was very nearly the same as that of 6 per cent acid. The charts on room temperature growth have likewise been omitted, because they do not reveal any significant differences from the observations at incubator temperatures.

Table II

I.P. Variant I



Saprophytic Strain I.P. (Variant I)

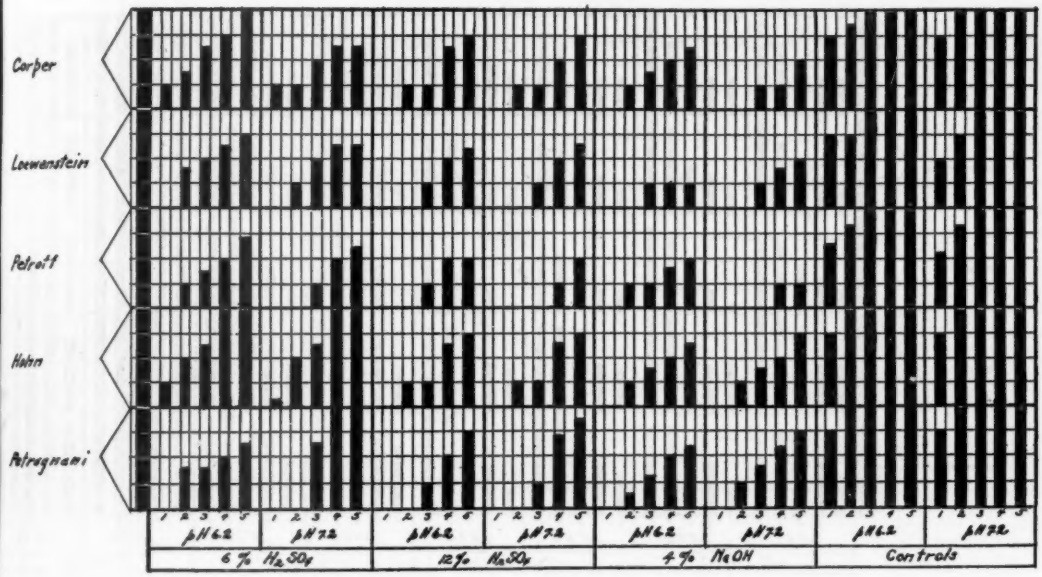
The two right hand columns of table II demonstrate that before digestion the microörganisms of this saprophytic strain grow well on all media. They are somewhat inhibited by digestion with 6 per cent sulphuric acid, more so by 12 per cent, and grow very poorly after 4 per cent sodium hydroxide.

Saprophytic Strain I.P. (Variant II)

Table III shows that these microörganisms likewise propagate well on all media before digestion. None of the digestants has as marked an effect as in the case of variant I, but here again 6 and 12 per cent sul-

Table III

I.P. Variant II



phuric acid digestion is slightly inhibitory while 4 per cent sodium hydroxide has the most marked inhibitory effect.

Strain M (Variant I)

Table IV

M. Variant I

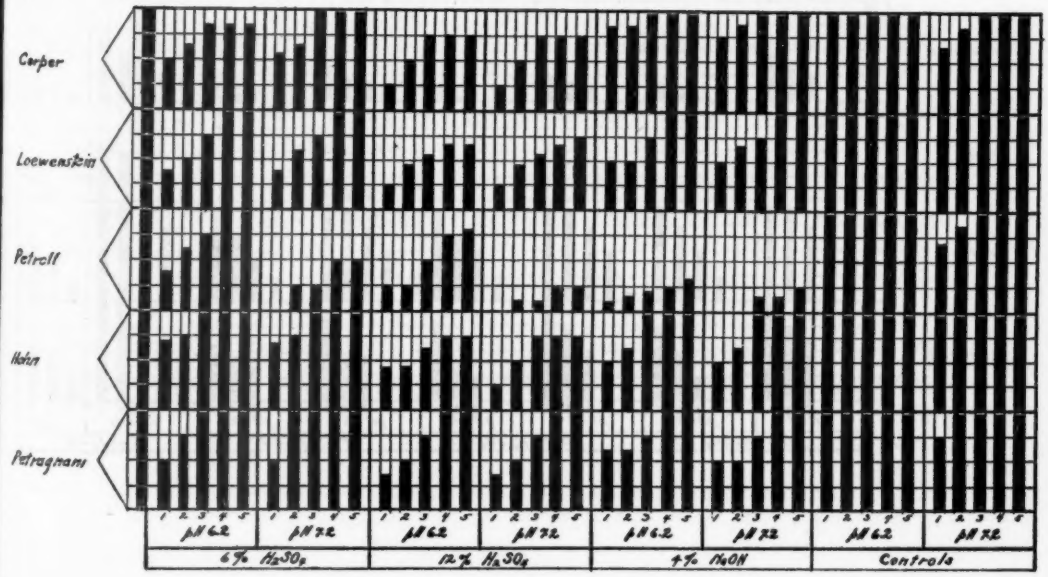


Table V

M. Variant II

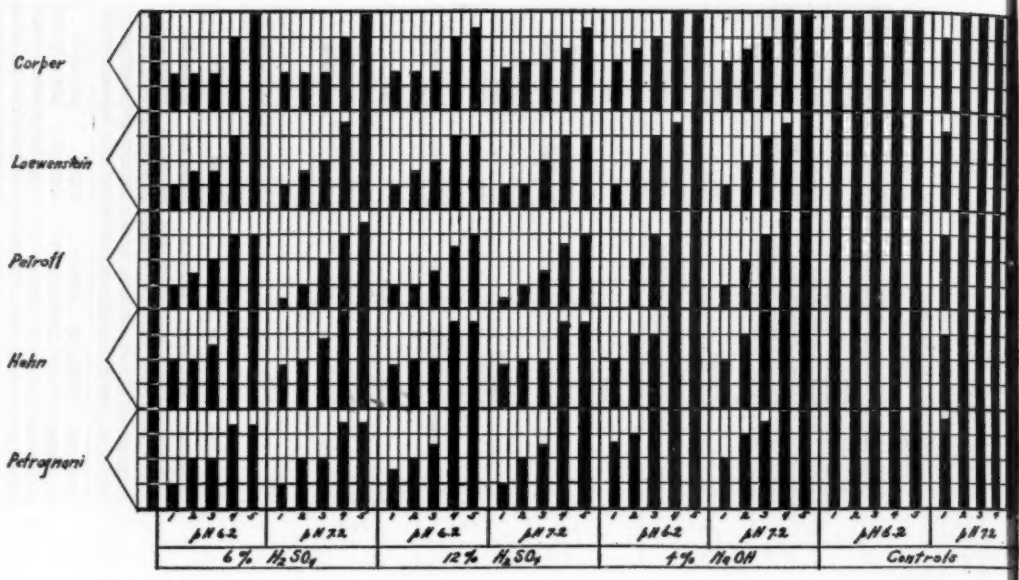
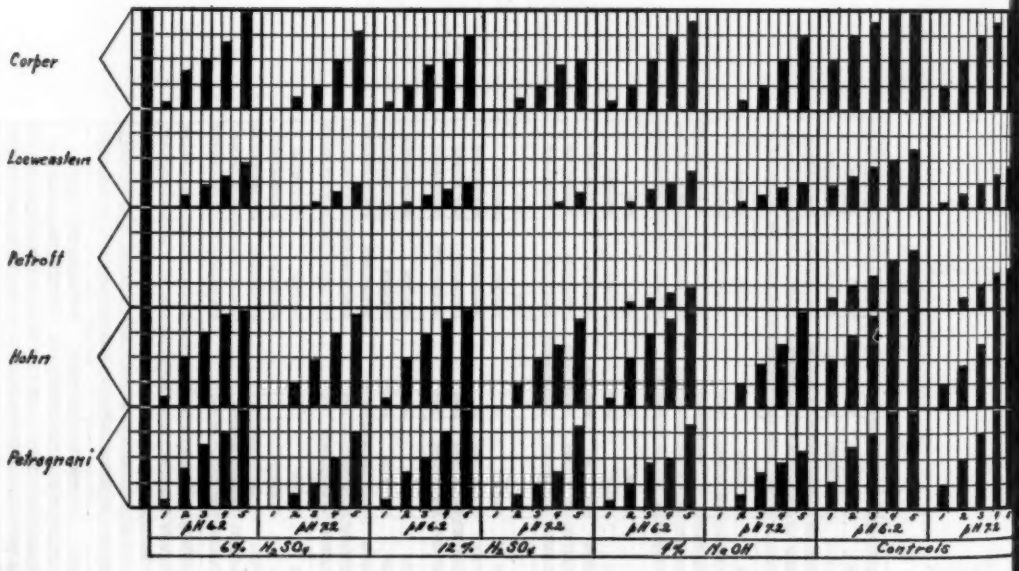


Table VI

H37 Rv



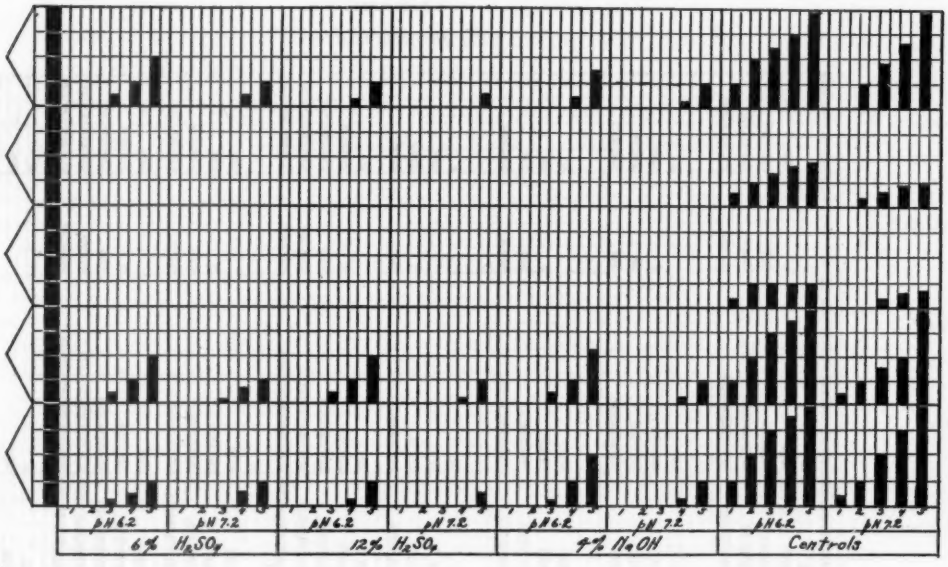
Strain M (Variant II)

The similarity in tables IV and V indicates that both variants of this strain are affected in practically the same degree by acid and alkali digestion.

H37 (Variant Rv)

Table VI demonstrates a new factor; at a pH of 6.2 the Rv variant

Table VII
H37 Ra



of this pathogenic strain grows better than at 7.2. It will also be noted that these microörganisms are unfavorably influenced by both the acid and alkali digestion and that none of the treated cultures propagate as well as the control material.

H37 (Variant Ra)

Table VII demonstrates that the nonvirulent (Ra) dissociate of the same strain of tubercle bacilli is even more fastidious and requires an

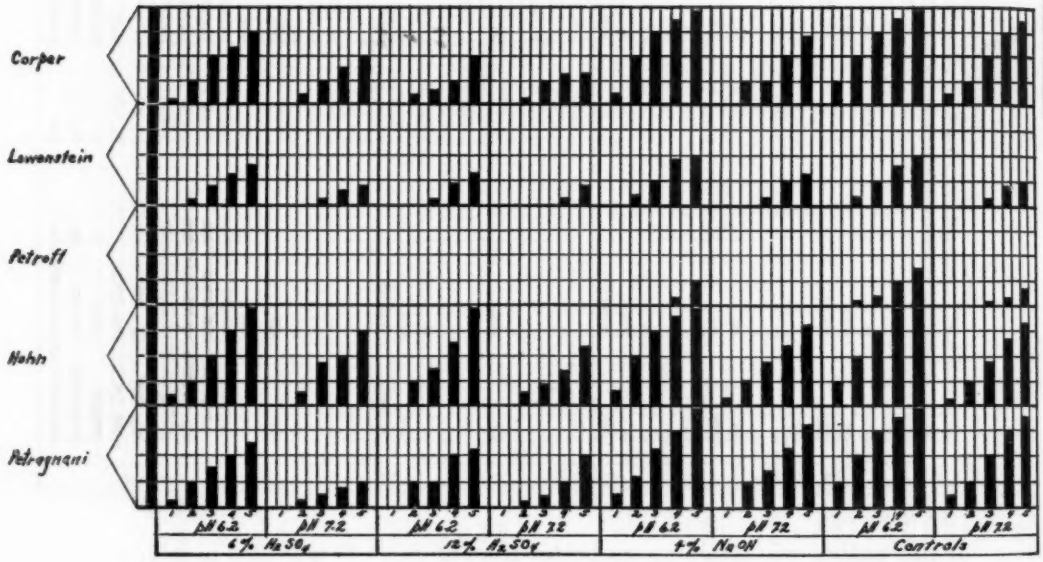
optimum environment for any growth to occur. Again it is evident that media of pH 6.2 produce the better growth, that digestion with sodium hydroxide is most detrimental, and furthermore that after digestion with either acid or alkali, neither Loewenstein's nor Petroff's medium will support growth.

R1 (Undissociated)

This microörganism was selected and studied on the various media because it is being used so extensively for experimental purposes. It

Table VIII

R1 Undissociated



does not manifest the marked attenuation that the H37 Ra has shown, but it seems to represent a strain of intermediate virulence. Any information as to its susceptibility to acid or alkali digestion, as well as its ability to propagate on the various media, would be of value.

Table VIII indicates that undissociated microörganisms of the R1 strain of tubercle bacilli grow less vigorously on any of the media than the H37 Rv, but somewhat better than the Ra. The poorest growths were obtained upon Petroff's medium and the best upon Hohn's. The microörganisms are unusually sensitive to the reaction of the medium,

a pH of 6.2 being much more satisfactory than one of 7.2. They do not react to digesting fluids in the same manner as the other strains, for appreciably more growth is obtained after treatment with 4 per cent sodium hydroxide than after 12 per cent sulphuric acid. The results would indicate that undissociated microörganisms of the R1 strain exhibit a behavior which is intermediate between that of the Rv and Ra variants of the H37 strain.

Acid-fastness: Neither variant of the H37 nor the R1 bacilli have exhibited any variation in acid-fast properties after treatment with acid or alkali digesting fluids. As all the cultures became older the microörganisms were less resistant to decolorization by alcohol containing 5 per cent nitric acid; to concentrations of less than 5 per cent however they were all equally resistant.

In the case of the saprophytic strains I.P. and M., there was definitely more resistance to decolorization by alcohol alone than by acid alcohol. The I.P. (I) variant which was most sensitive to environmental changes was decolorized most readily.

DISCUSSION

The application of these findings to the problem of detecting and culturing tubercle bacilli in exudates may be of considerable importance. Since one does not know the type and possible variant of acid-fast microorganisms which may be present in an exudate submitted for diagnosis, it seems not impossible that negative results may be gotten because the proper methods for detecting microörganisms were not employed.

In preparing smears, a routine decolorization with acid alcohol containing 5 per cent nitric acid may fail to detect bacilli that are only slightly acid-fast. In smears of material that has been previously digested with sodium hydroxide the acid-fast property is prone to attenuation. This may be the explanation for the occasional case of a positive sputum or urine culture after negative smears. The weakness of the acid-fast property in such microörganisms, or even their lack of virulence for animals, is not necessarily an indication that the microörganism is a saprophytic contaminant. They may equally well be Ra or Sa mutants of pathogenic types. One of us (W. S., Jr.) has derived a rough avirulent mutant (Ra) from a (Rv) culture of strain H37 originating from a single bacillus isolated by the Chambers method. Repeated transplantations on many media and animal passages have failed to alter the character of this mutant. In tuberculous exudates from

humans or animals, one should be on the lookout for such attenuated mutants of a low degree of acid-fastness. That they may not be overlooked it might be well to prepare a series of smears decolorized with alcohols containing different percentages of nitric acid from 0 to 5 per cent.

Since all strains of acid-fast microörganisms and even the different mutants of the same strain are not equally sensitive to different digesting fluids, it may also be essential to employ more than one reagent to remove contaminating bacteria. It is recognized that the addition of acid or alkali to microörganisms from a culture constitutes much more severe treatment than the application of the same substance to microorganisms protected in a heavy exudate, but as yet it is not known in how far the principles may apply to such exudates. It would probably be worth while to employ both acid and alkali digestants to any unknown diagnostic material. While Malkani (12) showed that the type of contaminants and the nature of the exudate governed the selection of the digestant, his calculations did not take account of the character of acid-fast microörganisms present.

Finally the type of medium appropriate to the growth of particular microörganisms has been shown to be of particular importance. Again, it is probably most profitable to employ more than one since the requirements of all microörganisms are not the same. It would seem more profitable to cut down the growth of secondary contaminants by the use of a proper digesting fluid than by the addition of some bacteriostatic substance like gentian-violet to the medium itself. Apparently gentian-violet inhibits the growth of certain types of tubercle bacilli, such as those of the R1 strain and H37 Ra variant as well as other microörganisms. The failure to obtain positive growths of R1 on Petroff's medium is well illustrated in a paper by Dowd (13) in which he reported several parallel series of cultures and animal subinoculations.

If one hopes to discover mutants of low virulence and of slight degrees of acid-fastness, he should employ culture media of several different types. Our results would suggest that if one is limited to one medium that the formula of Hohn, modified by adjusting the initial pH to 6.2, be followed.

SUMMARY

1. Acid-fast variants of known source have been subjected to digestion by sodium hydroxide and by sulphuric acid. The digested material has been subsequently cultured on different media.

2. Acid and alkali digestion affects the growth and acid-fast properties of some of the variants in a different manner from others.

3. It was observed that the microörganisms, especially the parasitic forms, grew much more rapidly on the media of pH 6.2.

4. The selection of the optimum media is essential for growing certain unstable forms of tubercle bacilli that have been somewhat weakened by the action of digesting fluids.

We wish to express our thanks to Dr. Edward R. Baldwin, Dr. Leroy U. Gardner and Dr. Fred H. Heise for their interest and many helpful suggestions in this problem.

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A MEDIUM FOR THE CULTURE, ISOLATION AND DISSOCIATION OF TUBERCLE BACILLI[1]

W. STEENKEN, JR. AND M. M. SMITH

In a previous study (1) on the cultivation of typical and atypical tubercle bacilli, it was observed that better growth was obtained on a medium of pH 6.2 and that, when it occurred, growth could be recognized sooner if the medium contained a nonbacteriostatic dye that would impart a dark background, preferably blue or black.

To fulfill these requirements a modification of Hohn's (2) medium has been worked out which possesses ideal characteristics. It is blue in color; it is not bacteriostatic; it contains the necessary growth promoting factors; and it retains its water on long preservation. Its formula is as follows:

Distilled H_2O	500	cc.
Na_2HPO_4	1.5	gm.
KH_2PO_4	2.0	gm.
$MgSO_4$	0.3	gm.
Mg Citrate	1.25	gm.
Asparagin	1.50	gm.
Glycerine	60.0	cc.

PREPARATION OF MEDIUM

The salts are dissolved in 500 cc. of distilled water at a temperature of about 80°C. The glycerine is added last and the mixture is sterilized in the autoclave at 10 pounds pressure for twenty minutes. This is the stock synthetic solution. To every 50 cc. of synthetic stock used, 4.4 cc. of a 1.0 per cent lacmoid[2] solution is then added; 163 cc. of whole egg mass is added making a proportion of synthetic dye egg mixture of 1 to 3 and the final concentration of lacmoid 1:5,000. This mixture is filtered through sterile gauze and the filtrate adjusted with N/1 hydrochloric acid, preferably with the aid of a potentiometer, to pH 6.0. The filtrate must be shaken thoroughly while adding the acid. It is now placed in tubes and inspissated for one and a half hours at 85°C. on two

[1] From the Research and Clinical Laboratory, Trudeau Sanatorium, Trudeau, New York.

[2] The lacmoid is made up in a 50 per cent alcoholic solution.

successive days. (The pH of the medium after inspissation becomes 6.2.) The medium may turn yellow on inspissation, especially in the deeper portions. This change in color is temporary, for on cooling the medium assumes its original blue color.

It has been the desire of most originators of media for the cultivation and isolation of tubercle bacilli to add a dye bacteriostatic for all microorganisms other than the tubercle bacillus. It has been our experience that practically all dyes incorporated in media to prevent the growth of secondary microörganisms have some inhibitory effect upon the growth of the tubercle bacillus. This inhibition is most pronounced when there are but few tubercle bacilli present in the material to be cultured.

It has also been observed that the digestion of the specimen is the most important factor in obtaining uncontaminated cultures. Careful digestion means vigorous shaking of the specimen with the proper concentration of sodium hydroxide or sulphuric acid until it is homogeneous and quite fluid, then incubation for one hour at 37.5°C.

It may be necessary to shake some specimens occasionally during this period of incubation to insure breaking up of clumps and allowing the digestion fluid to penetrate all of the material. Whatever time is spent in the preparation of the specimen for culture is well compensated for in the number of uncontaminated cultures obtained regardless of the dye incorporated in the medium.

APPLICATION TO DISSOCIATION

This modified medium has proved most satisfactory for dissociating the tubercle bacillus, since the lag period is shorter when compared to Hohn's, Petroff's, Petragnani's and Loewenstein's media. Colony structure is practically the same on all five media. Corper's[3] medium, which has been used by some investigators for dissociating the tubercle bacillus, gives as good growth as the modified medium. However, on the surface of this medium there are small yellow oily droplets in which the microörganisms grow and give rise to smooth mucoid appearing colonies. These colonies, when picked and subcultured to the same medium in an area free of droplets, give rise to typical Ra and Rv growth, showing that it is the physical effect of the droplets upon the growth and not true Sa or Sv growth.

For colony study of tubercle bacilli, we should like to recommend the Fisher culture tube no. 14–927. It requires much less medium than

[3] Final pH after inspissation pH 6.5.

Petroff flasks or bottles and at the same time has sufficient surface area for discrete colony formation. If one desires the removal of medium and colonies intact for photographing, it is easily accomplished by running the platinum wire around the outer edge of the medium.

SUMMARY AND CONCLUSIONS

A modification of Hohn's medium has been recommended. It differs from Hohn's in that it does not contain alanin; it contains only half the amount of asparagin; lacmoid is substituted for malachite-green to impart a dark blue background instead of the light green produced by malachite-green; it has an adjusted final pH of 6.2 as contrasted to Hohn's which is unadjusted but usually has a final pH between 7.1 and 7.3.

It has also been shown that the modified medium is preferable to Corper's medium for colony study since it eliminates marked atypical structures.

The use of the Fisher culture tube no. 14–927 is recommended for colony study.

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TUBERCULOMA OF THE LUMBAR SPINAL CORD[1]

EDWARD KUPKA AND RICHARD E. OLSEN

Tuberculoma of the spinal cord is one of the rare lesions produced by the tubercle bacillus. The cases reported in the literature have been almost evenly distributed in the cervical, thoracic, and lumbosacral portions of the cord.

In 1922 Thalhimer and Hassin (1) reviewed the literature and summarized the previous case reports. They credited Serre (2) in 1830 with the first reported case of tuberculoma of the spinal cord. Lebert (3) collected twelve cases in 1859, Herter (4) twenty-five in 1890, and Schlesinger (5) sixty-two in 1898. Thalhimer and Hassin excluded seventeen of Schlesinger's cases, found a total of sixty-seven proved cases, and added one. Fiamberti (6) in 1929 collected forty-eight cases, excluding those showing tuberculomata in the central nervous system other than in the spinal cord, and added one case.

Since the summary of Thalhimer and Hassin, the following reports of tuberculoma of the spinal cord have appeared:

Browning (7)	1921
Waring (8)	1921
Urechia and Elekes (9)	1922
Harbitz (10)	1922
Guizzetti (11) (two)	1922
Harris and Milliken (12)	1924
Dandy (13)	1925
Michelmore (14)	1925
Anderson (15) (three)	1928
Fiamberti (6)	1929
Kernohan, Woltman, and Adson (16)	1931
Weber and Logomarsiano (17)	1933
Jennings (18)	1934
Parmeggiani (19)	1934
Trabattoni (20)	1934
Hoeschel (21)	1935

These bring the total in the literature to eighty-seven.

[1] From the Oakland County Tuberculosis Sanatorium, Pontiac, Michigan.

Case Report

The present case is that of a white male, *N.T.*, aged fifty-nine. He was a die-maker by trade. His admission to the Sanatorium, June 22, 1936, was due to a pulmonary haemorrhage. The family history was not significant, and the source of his infection could not be traced. His health had been excellent until the present illness.

The first definite indication of disease occurred four years previously, when, without warning, he coughed up about a pint of blood. For several days he raised blood-streaked sputum. There were no further symptoms and the patient returned to work at once. Two years later he had a sudden attack of pain in the left lumbar region. This was diagnosed as lumbago, and he was given electrical treatments by an osteopath. The pain disappeared rapidly and did not return. Six months before admission a severe cold disabled the patient, and the productive cough, which began at that time, persisted. A physician told the patient that he had infected lungs, and recommended rest at home with plenty of sunlight. He lost fifteen pounds of weight and became weaker. Three weeks before admission he had a severe haemorrhage from the lungs, and a recurrence brought him to the Sanatorium.

On examination the man appeared rather younger than the stated age. He was neither pallid nor dyspnoeic, though he raised a little bright red blood with each cough. Breathing was chiefly abdominal due to bilateral restriction of the chest movements. Râles were heard in both upper lung fields. The diaphragm moved normally. There was no heart disease. The blood-pressure was 100/70. The liver edge extended two finger-breadths below the costal margin and was smooth and hard. There was no evidence of spinal cord defect at this time.

Laboratory studies showed a mild secondary anaemia, a negative Kahn test and a normal urine analysis. There was a high Gaffky count for tubercle bacilli in the initial and all subsequent sputum specimens. The roentgenograms showed involvement of the apex of the right lung to the second interspace, and a cavity in the left apex with involvement to the third interspace. The trachea and heart were slightly displaced to the left.

The haemorrhages ceased after strict bed-rest and did not recur. Sputum averaged 10 cc. daily, the cough was not severe, and there was no fever. One week after admission, a left phrenic exairesis was done, but although the diaphragm rose the cavity remained unchanged. An attempt to produce an artificial pneumothorax on the left was unsuccessful.

Toward the end of the first month the patient started to complain of pain in the left thigh posteriorly. This pain radiated to the left ankle. He said that the pain, which was continuous and made worse by motion, was similiar in character to the attack suffered two years previously. On examination the vibratory sense was found to be less in the left ankle than in the right. Pain,

touch, heat and cold sensations were normal. The patellar reflexes were equal. When the bed clothes rested directly on the skin of the left leg the patient complained that it felt as if "the hairs were being pushed into my skin." The possibility of cord involvement was considered, but the findings were too indefinite to permit diagnosis. Local heat and salicylates by mouth produced only temporary relief. The condition progressed, and in six weeks the pain involved the left lumbar region. There was a total loss of vibratory sense on the left ankle with slight impairment on the right. The patellar reflexes were weakened bilaterally with the left responding less than the right. Touch sensation was lost below the mid-thigh on the left and below the knee on the right. Ankle clonus could be elicited on the left. The abdominal reflexes were impaired on the left.

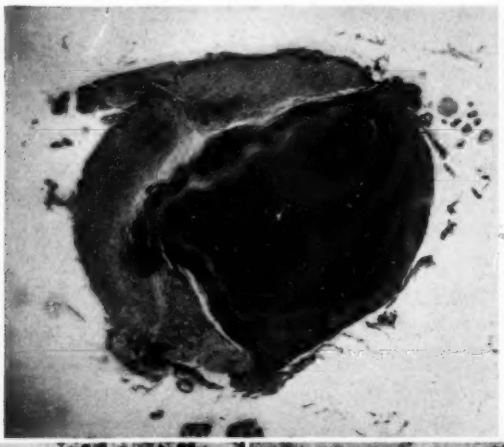
As it seemed probable that a spinal cord tumor was present, the patient was transferred to the University Hospital at Ann Arbor for further diagnosis and specific treatment if indicated. During the five weeks' stay there the patient developed tenderness to firm pressure over the fourth and fifth lumbar and first sacral vertebrae, and foot drop with almost complete paralysis of the left foot. The spinal fluid was normal and the pressure was not increased. A roentgenogram of the spine was interpreted as showing minimal generalized hypertrophic spondylitis. Partial obstruction of the spinal canal in the lower dorsal region was diagnosed by lipiodol injection. The progressive severity of the pulmonary condition would have prevented any operative interference by the neurosurgeons, had they been so inclined.

After five weeks the patient was returned to the Sanatorium. A marked change was evident. He could no longer walk or even bear his weight on his left leg, which was noticeably atrophied. He was incontinent of faeces, and a catheter was necessary to overcome urinary retention. Coughing was severe and he had difficulty in raising sputum, which had increased in amount. Daily fever was present. A decubital ulcer appeared over the sacrum, and râles were heard in the bases of both lungs. The patient complained most of pain in the lower lumbar and sacral regions, and no longer of pain in the lower extremities. Death occurred rather suddenly on November 18, 1936, five months after first admission.

Autopsy: Decubital ulcers were present over the sacrum and on the toes. The skin was flabby and the extremities showed wasting atrophy. Gross examination of the spinal cord showed no lesion until after it was fixed and cross sectioned. Then a necrotic area was found in the mid-lumbar cord, which had destroyed most of the gray and white matter over a distance of one centimetre. Microscopically this was found to be a caseating tuberculoma, completely necrotic in the centre, with a border of epithelioid and Langhans' giant cells. The Ziehl-Neelsen stain showed fairly numerous tubercle bacilli scattered through the periphery of the necrotic mass. The tuberculous process

extended up to, but not through, the pia mater. The tuberculoma was located in the left ventral part of the cord, but was so large that the cord was almost

FIG. 1



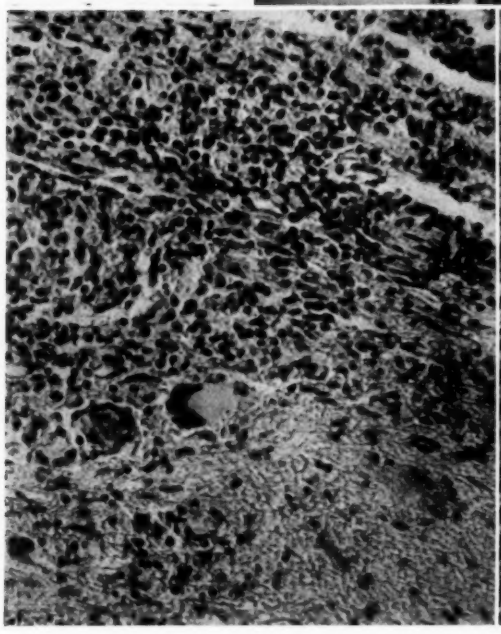


FIG. 2

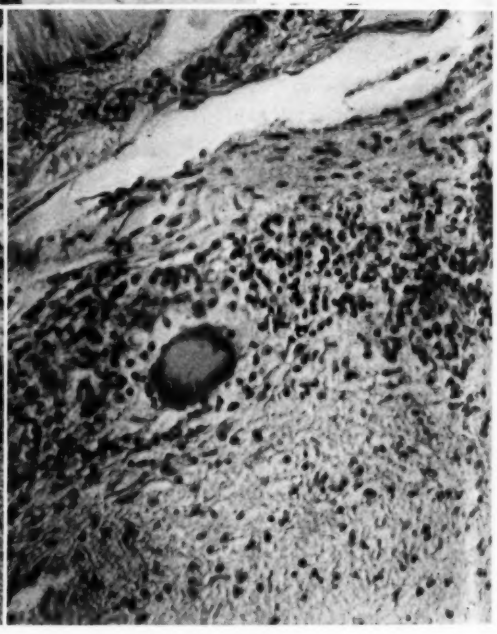


FIG. 3

FIG. 1. Cross section of the tuberculoma in the spinal cord. ×5
FIG. 2. Zone of lymphocytic infiltration about the caseous mass. ×250
FIG. 3. Involvement of the pia mater by the tuberculoma. ×250

completely destroyed at this level. No other evidence of tuberculosis was found in the cord or meninges. There was considerable congestion of the meninges and dorsal ganglia, with some mononuclear infiltration but no tubercle formation. In the apex of the left lung was a large cavity with an active tuberculous process about it. There were old miliary tubercles scattered through both lungs, with a fresh miliary spread which involved the spleen, liver and kidneys, as well as the lungs. The cardiovascular system was within normal limits for the age of the patient. There was a small agonal haemorrhage into the loose tissue about the upper pole of the right kidney. There was no gross or microscopic evidence of gastrointestinal tuberculosis. The little remaining adipose tissue had undergone serous atrophy.

There was no evidence of healing in the spinal cord tuberculoma, and no relation to the attack of lumbago two years before admission could be demonstrated from the autopsy material.

SUMMARY

While under observation, a patient suffering from pulmonary tuberculosis, developed symptoms of a lumbar spinal cord lesion. At autopsy this was found to be a tuberculoma of the mid-lumbar cord.

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EDITORIAL

The Purification of Tuberculin

In this issue of the REVIEW appears an article by Florence B. Seibert, Kai O. Pedersen and Arne Tiselius (1) entitled *Molecular Weight, Electrochemical and Biological Properties of Tuberculin Protein and Polysaccharide Molecules*. Since this article represents the culmination of more than a decade of research by Doctor Seibert, research recognized by the award of the Trudeau Medal of the National Tuberculosis Association, special notice of the investigation and its place in the larger picture of scientific inquiry on tuberculosis seems warranted.

Of all fields of tuberculosis research few, if any, have been cultivated more continuously and intensively than that of tuberculin and the reaction it causes. Tuberculin is of three-fold significance for physicians and investigators of the problems of tuberculosis. It is best known as the means to a specific test for the existence of tuberculous infection. Secondly, in one form or another, it has been widely used in the treatment of tuberculosis. Finally it is a substance of basic importance in the pathological process of tuberculosis itself, for it is elaborated in the tuberculous body, and a variety of the manifestations of the disease are referable to this substance and the effect it has produced upon the diseased body.

These facts justify intensive study of the nature of the substance. Protracted research since the discovery of tuberculin by Robert Koch has shown how difficult the problem is. Because of its importance and its difficulty of solution without special support, the problem was selected years ago by the Committee on Medical Research of the National Tuberculosis Association for thorough investigation. Ten years of study by Doctor Seibert and associates in America, supported by a grant from the National Association, yielded abundant information of much value on the substance and the nature of its action. By that time it had become clear that a series of products with tuberculin activity are present in the tubercle bacillus and the culture medium on which it has grown, alike, however, in that they are either complete proteins or derivatives thereof. The fact that all these products, on the basis of equivalent weights, are

of identical potency made it seem highly probable that they came from a parent substance, owing its total activity to the summation of activity of its component parts. Since biological activity persisted in spite of considerable degradation of active substances of apparently high molecular weight, it was of obvious interest to follow the degradation to the point where activity ceased, with the hope that tuberculin activity could finally be traced to a chemical compound, or even part of a chemical compound, of easy chemical understanding. Out of this phase of the investigation came the Purified Protein Derivative of Tuberculin, widely known and extensively used as a standard substance for the tuberculin test.

The very name given to it indicates, however, the incompleteness of the research out of which it was developed. It was easily proved to be the active principle of Old Tuberculin. Indeed it must be recognized that it merely represents the highly complex and variable Old Tuberculin in simple, constantly reproducible form, freed from extraneous substances. It was proved to be incapable itself of producing antibodies, although potent in eliciting a skin reaction, therein apparently falling among the group of substances of immunological significance known as haptenes. Eliciting no antibodies itself it was perfectly adapted to the skin test, since positive reactions in repeated tests could not be referred to its own action; in this respect it differed from its apparent parent substance, the large protein molecule of the tubercle bacillus, which not only elicited the reaction in an infected man or animal, but itself brought about a sensitized state that might be confused with true infection. The final proof for the place of the Purified Protein Derivative among antigenic substances was given by Doctor Seibert herself when she combined it with an inert colloidal substance and thereby converted it into a complete antigen, eliciting both skin reaction in the infected animal and antibody production in the normal animal.

This advanced state of research still left unsolved the problem of chemical structure of the group of substances with tuberculin activity and the chemical reasons for the above noted variation in biological effect. Unable to obtain the necessary information through the means available in her own laboratory Doctor Seibert turned to one of the masters of protein chemistry and the facilities of his laboratory, Prof. The Svedberg, Director of the Institute of Physical Chemistry, Upsala, Sweden, Nobel Prize winner in chemistry in 1926. In the course of a year's study in the latter institution, mediated by a fellowship from the John Simon Guggenheim Foundation, in coöperation with Doctor Pedersen and Doctor

Tiselius, she succeeded in advancing our understanding of tuberculin notably. The abridged article[1] in this number of the REVIEW summarizes the results obtained. A variety of substances of biological importance were secured in that state of purity fulfilling the most rigid requirements of modern physical chemistry. Without going too far into technical details it will suffice to say that the proof of purity lay in demonstration of complete homogeneity in molecular weight as shown by the elaborate Svedberg centrifuge, and homogeneity in chemical character as shown by the method of electrophoresis.

It is of interest to note that a substance with complete antigenicity, both in the production of antibodies and in the elicitation of serum and skin reactions, was obtained, and that this possessed a molecular weight of approximately 32,000, the size postulated by Svedberg himself as the unit of protein structure in general. The relation of this to other products with tuberculin activity was suggested by Doctors Seibert, Pedersen and Tiselius. They isolated large heterogeneous substances, possibly derived through polymerization of the protein unit, and a homogeneous molecule of 16,000 molecular weight, presumably resulting from splitting of the protein unit into equal parts.

It was not surprising to Doctor Seibert to find that the "Purified" Protein Derivative itself was not perfectly pure, but contained substances with large and small molecular weight in addition to the main bulk of the product, which possessed a molecular weight of 16,000. The latter substance is presumably the true Purified Protein Derivative or PPD. No serious reflection is thus cast upon the present practical use of the Purified Protein Derivative as a standard, for its potency is unaffected by its slight admixture with these substances, themselves of tuberculin potency. It is worth noting, however, that the method discovered, admittedly of inordinate expense for practical operation at present, permits the isolation of an apparently chemically pure PPD.

In the meantime it is to be noted that the elaborate investigations carried on through the National Tuberculosis Association's Committee on Medical Research, aside from the sustained interest in this country, have aroused increasing attention abroad. The Institute of Physical Chemistry itself has been provided with funds for continued work in this field. A group of British investigators (2, 3) have repeated the American work with characteristic thoroughness and pronounced the Purified

[1] The full details of the investigation appear in the Journal of Experimental Medicine, September, 1938.

Protein Derivative the "most suitable agent for the Mantoux test, and the best reagent so far produced for diagnostic tests in man." T. Madsen, Director of the State Serum Institute of Denmark and Chairman of the Health Committee of the League of Nations, in an address before the Annual Meeting of the State and Local Committees on Tuberculosis and Public Health of the State Charities Aid Association of New York (New York City, May 11, 1937), in discussing the standard tuberculin of the League of Nations, referred to the stability and constancy of the Purified Protein Derivative; he also described similar work in the state laboratories in Copenhagen under his own direction, carried out by K. A. Jensen and associates, and aimed at the production of a pure international standard, which has resulted in a modified method of preparation of the same substance. In their published report Jensen and his colleagues (4) have proposed the preparation of an international standard purified tuberculin of the same strength as the Purified Protein Derivative or their corresponding Danish preparation.

These facts emphasize the recognition by responsible bodies of the wisdom in practice of using pure standard products in tuberculin testing. In still broader aspect, however, the long investigation on the purification of tuberculin is to be judged as a contribution of significance in the widening field of exact understanding of products of great biological importance. The last few years have witnessed brilliant chemical work leading to well defined knowledge of the vitamines, the hormones and the carcinogenic agents. It can truly be said that in our efforts to understand the fundamental mechanisms of disease, research in tuberculosis keeps pace with this notable advance in other fields of medicine.

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E. R. L.

Pol N. Coryllos

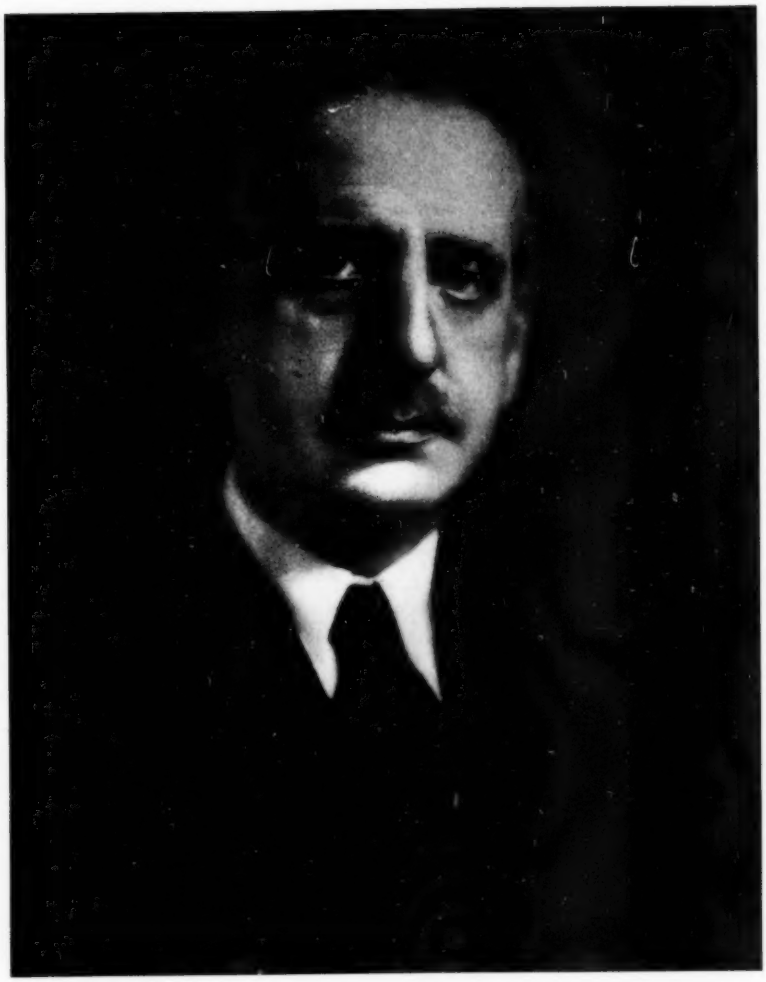
1880–1938

On July 26, 1938, died after a short illness, terminated by a sudden cerebral accident, Pol N. Coryllos, thoracic surgeon, physiologist, inquisitive searcher of truths. The world is poorer for his loss.

Doctor Coryllos was born in Patras, Greece, in 1880. After his graduation from the College of Athens (B.A.), he obtained his medical degree from the Medical College of the National University of Athens in 1900. He then went to Paris, where he obtained his B.S., M.S. and Ph.D. from the Sorbonne, and a second medical degree from the Medical College of the University of Paris in 1914. During this time he served as Instructor of Anatomy (1902–1910), of Pathology (1909–1911), and Assistant in Gynecology (1910–1912) under Dr. Jean Louis Faure. In 1912, during the Balkan War, Doctor Coryllos returned to Greece as a volunteer. He was commissioned as Captain in the Medical Service of the Greek army and appointed director of an ambulance unit composed of seventy-five beds. This he organized as a mobile hospital, thus bringing the surgical hospital to the wounded, which was contrary to the established custom of transporting the wounded to the hospital. This unit established by Doctor Coryllos was the precursor of the medical organization later used during the World War. Thus was he able to treat surgically, and within a few hours after injury, abdominal, thoracic and skull wounds. His experiences were published in a number of articles and in book form in Paris in 1914, under the title of *Preventive Trepanation in Bullet Wounds of the Skull.* For this he was awarded the Gold Medal from the Medical Academy of Paris.

At the end of the Balkan War he resumed his hospital position in Paris (1913). In 1914 he was Lieutenant in the French army. He served at Dieppe, Bar le Duc and Verdun from August, 1914 to December, 1916.

In December, 1916, he was sent by the French Government as a member of a Special Mission to Russia to organize the surgical service at the Russo-Rumanian front. He was given the medical direction of the division of Padureni, where he organized the mixed front hospitals, Russian and Rumanian.



Pol N. Corylios
1880–1938

In March, 1918, he was recalled to France, promoted to the rank of Major and served at Chateau Thierry until the Armistice (1918).

Immediately following the Armistice, at the request of the Greek Government, he was sent to Greece on a Special Mission to organize the surgical service in the Greek army, where he remained until 1922, with the rank of Surgeon General. During this time he devoted himself to the study of wounds of the chest, for which he had organized a special surgical centre.

In 1919 he was appointed Professor of Surgery in the Medical College of the National University of Athens, from which he had graduated nineteen years before.

The decorations which Doctor Coryllos received from the various countries he had served are a slight index of the value of his work during this period. From France he received the Croix de Guerre and the Cross of the Legion of Honor; from Greece, the Cross of Savior (Officer and Commander), the Cross of Valor, the War Cross for Distinguished Services and in 1936 the Gold Cross of the Redeemer (Commander); from Serbia, the Cross of the Savior (Officer); from Rumania, the Cross of the Rumanian Star (Officer), the Cross of Distinguished Services and the Cross of Queen Marie; from Russia, the Cross of St. George, the Cross of St. Vladimir (Commander), the Cross of St. Stanislaus (Commander) and the Cross of St. Ann's (Commander).

In 1923, by which time Doctor Coryllos was in New York, he was appointed Professor of Clinical Surgery at the Medical College of Cornell University, which position he held until his death.

His activities in this part of the world were closely related to the investigation of the surgical treatment of thoracic diseases, with which specialty he finally became completely identified. At the time of his death Doctor Coryllos was Director of Thoracic Surgery at the Metropolitan Hospital and Sea View Hospital in New York and the United States Veterans Hospital at Castle Point; Associate Surgeon and Director of Thoracic Surgery at the Polyclinic Hospital; Consultant Thoracic Surgeon at the Broadstreet Hospital, Staten Island Hospital, Beth Israel Hospital of Newark and Vassar Brothers' Hospital at Poughkeepsie; Consultant Surgeon to St. Luke's Hospital at Newburgh, New York; and Director of Thoracic Surgery at the Manhattan General Hospital.

Mere recital of accomplished deeds gives but lip service to the true qualities of the man. Product of a cosmopolitan world, schooled in the turbulent progression of an active life, his scintillating intellect shone

forth with a polished brilliance. His keen analytical mind and searching inquisitiveness led him at times to unorthodox conclusions which he would defend with diplomatic but devastating logic. His open mind brooked no compromise with truth. He was ever willing to discard the old when proved wrong, and he expected others to do likewise. His limitless energy drove him on relentlessly in the zealous pursuit of his life work. His flair for leadership and the stimulation of his brilliant personality attracted to his banner a group of men, many of whom, having partaken of the celestial fire, are already carrying the torch to worlds of their own. His truly was the fruitful life. Perhaps no more fitting epitaph for the man can be found than the following quotation, which sums up the essence of all that was Pol Coryllos:

I brook no monotone in life,
No idle hours;
I stride on edges of a knife
And not on flowers.
I gather tirelessly a crop
Of word and line
And filter each begotten drop
Like costly wine.

D. U. and G. G. O.

ACETONE EXTRACT OF TUBERCLE BACILLI[1,2]

Its Influence on the Isolation and Virulence of Human Strains of Tubercle Bacilli

L. NÈGRE AND J. BRETEY

During the experiments resulting in the preparation of methylic antigen, Boquet and Nègre showed that the bacillary substances insoluble in acetone and soluble in absolute methyl alcohol exert a retarding action on the evolution of experimental tuberculosis in laboratory animals. In contrast, the substances soluble in acetone activate it considerably.

In accordance with this last evidence, we thought with Valtis, van Deinse, and Beerens, that the subcutaneous injection of acetone extract of tubercle bacilli could be used as a diagnostic method in cases where the presence of tubercle bacilli in pathological specimens is difficult to demonstrate.

The technique used is as follows:

Preparation of Acetone Extract of Tubercle Bacilli, Called Simply E.A.B.T.

Cultures of human and bovine strains of tubercle bacilli on glycerin broth of six weeks' growth are sterilized at 120°C. in the autoclave. The cultures are filtered through paper which retains the bacillary bodies, which are subsequently washed in physiological saline and dried at 37°C. in the incubator. After the residue is weighed, it is placed in a flask with acetone in the proportion of 0.01 gm. of bacillary body to 1 cc. of acetone, and glass beads are added to the flask and the contents shaken from time to time. It is then allowed to stand 48 hours, and filtered again through paper. The filtrate contains the acetone extract. To prepare for injection, an equal part of distilled water is added to the filtrate, and the acetone is distilled off by heating to 40°–45°C. When the amount of fluid has returned to the original volume, all the acetone will have disappeared. The waxy and fatty bacillary substance in suspension is then injected subcutaneously into the animal, 1 cc. of solution being used.

[1] From the Institut Pasteur, Laboratoires de recherches sur la tuberculose, Paris.

[2] Translated by André Cournand.

Technique of Inoculation

The specimen suspected of containing tubercle bacilli is inoculated subcutaneously in the groin of at least six guinea pigs. Three of these animals are treated twice a week with subcutaneous injections of 1 cc. of E.A.B.T. for two months following inoculation. The others are used as controls. An essential precaution in injection is the use of separate needles and syringes for each guinea pig, to avoid the possible transport of any preëxisting microörganism from one animal to another.

In cases where growth on Loewenstein or Petragnani media and guinea-pig inoculation gave negative results even after six months' observation, lesions could be demonstrated in guinea pigs inoculated with the same products and treated with biweekly injections of E.A.B.T. for a period of two months.

When microcoscopical examination is made for tubercle bacilli in the tissue smear of lymph nodes of these animals, one must bear in mind that the acetone extract, in spite of the filtration to which it has been subjected, always contains some bacillary debris. This debris, retaining its acid-fast property, can occasionally be found on the slides. But these elements are more or less changed, scattered or fragmented, and should not be confused with living bacilli, slender and grouped, which are in the process of multiplication in the lymph nodes. One should rely only on the culture from the lymph nodes of treated guinea pigs.

Results with Products of Different Origin

With 41 products of diverse origin (sputum, pus, serous exudate, urine), in which inoculation alone gave negative results, we have had 5 positive results by the method of injection with E.A.B.T. (2 urines, 1 pleural fluid, 1 hydrocele of the tunica vaginalis, 1 synovial fluid).

The strains obtained by culture on Loewenstein media from the guinea-pig lesions thus treated, showed in 4 cases rough colonies virulent for guinea pigs, and in 1 case smooth colonies.[3]

In our laboratory, Beerens showed that in guinea pigs inoculated with the blood of a tuberculous patient, and treated with E.A.B.T., tuberculous lesions developed, although the same specimen of blood in control animals gave negative results. By culture of these lesions on Loewenstein media, Beerens has isolated rough strains of tubercle bacilli, virulent for guinea pigs.

[3] The smooth colonies thus isolated, resembling somewhat avian tubercle bacilli, will not be discussed further in the present work.

Experimental Study of Bacteraemia by the Method of Injection with E.A.B.T.

We have studied by this method tuberculous bacteraemia in guinea pigs previously inoculated with .01 mg. of a strain of known human origin (strain Bar.).

At different intervals after virulent inoculation, the blood of these animals has been withdrawn aseptically by cardiac puncture, and an injection of 2 cc. made subcutaneously in 5 guinea pigs. Three were treated during two to two and a half months subcutaneously biweekly with 1 cc. of E.A.B.T., and 2 were used as controls and sacrificed six months later.

The results were as follows:

Interval between virulent inoculation and withdrawal of blood	*Tuberculosis in guinea pigs inoculated with blood and not treated with E.A.B.T.*	*Tuberculosis in guinea pigs inoculated with blood and treated with E.A.B.T.*
7 hours	0	0
24 hours	0	+ (strain Bar. 1)
3 days	0	0
7 days	+	+
15 days	+	+
25 days	0	0
29 days	0	+ (strain Bar. 29)
77 days	0	0
84 days	0	+ (strain Bar. 84)

We have obtained by inoculation alone 7 negative and 2 positive results from withdrawal of blood on the seventh and fifteenth days after inoculation.

During the period when controls gave negative results (before the seventh and after the fifteenth day) we have had 3 more positive results, at the twenty-fourth hour, at the twenty-ninth day, and at the eighty-fourth day, in E.A.B.T.-treated guinea pigs which were inoculated with the same specimen of blood.

In these 3 cases the strain isolated (strains Bar. 1, Bar. 29, and Bar. 84) showed rough colonies virulent for guinea pigs, and in rabbits it produced a miliary pulmonary tuberculosis after intravenous injection of .01 mg. It was not virulent for the hen.

Thus we have been able, in 3 cases out of 7 (42.8 per cent) when the search for tuberculous virus in the blood of a tuberculous animal was negative, to prove its presence after inoculation in an E.A.B.T.-treated guinea pig.

Valtis and van Deinse have obtained similar results by the same method. On the other hand, Lanza examined 8 negative sputa, 4 exudates from artificial pneumothorax, and 8 tuberculous bloods by subcutaneous inoculation with and without E.A.B.T. treatment and by inoculation into the lymph nodes of guinea pigs (following Ninni's method). With sputum, in 2 cases when subcutaneous inoculation alone was negative, Lanza found positive results in E.A.B.T.-treated animals or inoculated into lymph nodes. The 4 pleural fluids infected the guinea pigs by subcutaneous inoculation. With the specimen of blood, all the single subcutaneous inoculations were negative. On the other hand, in 3 cases (37 per cent), this author obtained a positive result for tuberculosis in E.A.B.T.-treated guinea pigs. In only 1 of these 3 cases the result had been equally positive by the single inoculation into lymph nodes.

It appears from all these results that this method of injection sometimes shows evidence of the tuberculous virus in certain pathological specimens (blood, urine, serous exudate), although the direct inoculation of the guinea pig alone, a method up to the present considered efficient, had failed with these specimens.

Characteristics of Tubercle Bacillus Strain, Rough Colonies, Isolated by this Method

In studying the pathogenicity of the strains of rough colonies of tubercle bacilli thus isolated, we, as well as Valtis, van Deinse, and Beerens, have been impressed by the fact that in spite of its human origin it shows in most cases at the time of isolation a virulence much greater for the rabbit than the bacilli of the classical human type.

In rabbits having received intravenously .01 mg. of these strains recently isolated, one frequently finds a miliary pulmonary tuberculosis, sometimes even nodules in the spleen and kidney, which will occasionally heal.

In general, these strains lose their exaggerated pathogenicity for rabbits after several subcultures on artificial media, and recover the character of a classical human tubercle bacillus.

We have followed for more than four years the variations in virulence for the rabbit of 3 strains, Bar. 1, Bar. 29, and Bar. 84, isolated from the blood of a guinea pig inoculated with a strain of human origin (strain Bar.), of which the virulence had previously been established. Guinea

pigs were injected subcutaneously with .000,01 mg. Rabbits inoculated intravenously in doses of 0.1 mg. to 1.0 mg. showed no lesions.

The pathogenicity for the rabbit of strain Bar. 29 was weak, although more pronounced than the original strain (Bar.). In the lungs of rabbits inoculated intravenously with 1 mg. and sacrificed one month later, a scattering of small nodules was noticed; in rabbits having received .01 mg. by the same route, only a few tubercles were seen at the base of the lungs. After three months of subculture, this strain no longer produced lesions in the rabbits with intravenous inoculation of 1 mg. or .01 mg.

During the first two years following their isolation, Bar. 1 and Bar. 84 inoculated in several instances intravenously, .01 mg., always produced within a month confluent lesions in the lung, with rather numerous granulations in the kidney and sometimes in the liver and spleen. However, these strains by intrapleural inoculation of .01 mg. into the rabbit[4] behaved not like bovine, but like human bacilli. They showed besides, as regards the pH in Sauton's medium, the same reaction as the original strain, varying from the sixth to fiftieth days, from 7.5, 7.6, 7.5, 6.8 to 5.8.

The strain Bar. 84 still retains, after four years of subculture, the pathogenicity which it always showed for the rabbit, on intravenous injection of .01 mg.; strain Bar. 1 lost it after two years of subculture. On the other hand, the virulence of these two strains for the guinea pig remains the same as that of the original strain. It infects the guinea pig by subcutaneous inoculation of .000,01 mg.

CONTROL EXPERIMENTS

This last fact permits us to believe that our experiments have not been influenced by a bovine bacillus preëxisting in the body of the guinea pig or introduced by inoculation.

The strains Bar. 1, Bar. 29, and Bar. 84 have not the characteristics of the bovine tubercle bacillus, but should such be the case, it would be surprising if one after the other lost its virulence for the rabbit, while the virulence for the guinea pig did not vary.

Furthermore, the control experiment which has been undertaken by us with Gerhardt, Valtis, and van Deinse, also by Saenz, Costil, and

[4] According to Boquet and Laporte, generalized tuberculosis follows the intrapleural injection of a dose of .01 mg. of a bovine strain in rabbits. In contrast, not even localized pulmonary or pleural lesions at the site of the injection are observed with human strains, introduced in the same amount and by the same route.

Sadettin, has shown, except for the most unusual cases of spontaneous tuberculosis in the guinea pig (we have observed 2 cases in 700 in our experiments), that there is no doubt as to the origin of the rough strain of tubercle bacilli obtained by our method.

In a total of 410 guinea pigs not previously infected which were treated with E.A.B.T. during a long period of time, we, as well as our colleagues, have never isolated rough colonies of tubercle bacilli, virulent for guinea pigs, by culture of lymph nodes or spleen on Loewenstein media.

One of us, in collaboration with Valtis, tried to determine whether in laboratory animals, inoculated with human type tubercle bacilli, the prolonged treatment with E.A.B.T. could modify the pathogenicity of this microörganism for the rabbit.

We have shown that in rabbits inoculated intravenously with .01 mg. of tubercle bacilli of the human type the rare pulmonary lesions are not activated by the subcutaneous biweekly injection of 1 cc. of E.A.B.T. If the treatment is given by the intravenous injection of 2.5 cc. of the extract, repeated four times a week, following the virulent inoculation, there is observed in certain cases a slight activation of pulmonary lesions, especially if the dose of the bacillus is doubled, .02 mg. in place of .01 mg. The successive passage of these strains in rabbits given repeated intravenous injections of E.A.B.T. did not increase the pathogenicity of human tubercle bacilli for the rabbit. Furthermore, the pathogenicity of BCG or avian tubercle bacilli, following intracutaneous injection of 10 mg. in guinea pigs, was not modified by the use of E.A.B.T. The question of the mode of action of acetone extract injections remains an open one.

CONCLUSIONS

In guinea pigs inoculated with specimens suspected of being tuberculous, the treatment of these animals for about two months with semiweekly injections of E.A.B.T. causes the tuberculous lesion to appear in cases where control guinea pigs inoculated with the same specimen remain negative.

This method has given us positive results especially in cases where inoculation has been made with blood, serous exudate, or urine. In most cases the strain of tubercle bacilli isolated by culture on egg media from guinea-pig lesions produced by specimens of human origin show for the rabbit a virulence which is not in general that of the human type of tubercle bacilli. It is nonpathogenic for the hen.

Although the virulence of the bacilli for the guinea pig does not vary, for the rabbit it disappears in a few months following isolation.

In 3 cases we have isolated by the same method strains of tubercle bacilli from the blood of a guinea pig inoculated with a known human type of bacillus, although inoculation with the same specimen of blood in the control guinea pig remained negative.

In 1 case the strain thus isolated had a virulence for the rabbit slightly more pronounced than that of the original strain, but lost it rapidly.

The other 2 strains had a virulence much more pronounced for the rabbit. One of these strains retained it for two years. The other still possesses it four years after isolation. However, from all other points of view, the 2 strains behave like other strains of human type of tubercle bacilli.

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BODY SECTION RADIOGRAPHY WITH THE LAMINAGRAPH IN PULMONARY DISEASE[1,2]

SHERWOOD MOORE

Body section radiography is a type of X-ray examination whereby a particular section, plane, or layer can be visualized with more or less complete exclusion of other layers. This term is desirable because there are many methods of accomplishing this, and several types of apparatus for doing so. In consequence, there are a number of more or less synonymous terms used to describe methods and apparatus thus far developed. All of them are based on approximately the same fundamental physical principle.

This physical principle is one in which, during exposure, a synchronized, coördinated movement of X-ray tube and film takes place about a fixed axis in such a way that shadows of objects in this axis maintain a constant relationship to film and tube, while objects not in this axis have a shifting relationship so that their shadows are dispersed. The tube and film can be made to move in opposite directions or in the same direction but out of phase.

Though the basic principle was developed as long ago as 1921 by Bocage (3), its practical application to radiography did not take place until 1930 by Vallebona (10). He was followed by Ziedses des Plantes (11, 12, 13) in 1931, and by Chaoul (4) and Grossmann (5) in 1935, the latter developing a very efficient apparatus. Vallebona called his apparatus the stratigraph, and it could be used in two ways: either the tube and film could be moved on an arc with the patient stationary, or the tube and film remained fixed and the patient revolved. Ziedses des Plantes developed a coördinated movement of film and tube, with either a circular or an Archimedean spiral action. He called his method planigraphy. In the Chaoul and Grossmann apparatus, the tube at the end of a pendulum moves on an arc and the film in a horizontal plane. This apparatus is known as the tomograph.

[1] Presented at a session of the Clinical Section at the 34th annual meeting of the National Tuberculosis Association, Los Angeles, California, June 22, 1938.

[2] From the Edward Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri.

So far two methods of radiographing a selected layer have been described, one in which tube and film move and the object is stationary, and the other in which the reverse is the case, tube and film being stationary and the patient revolved. At the Fifth International Congress of Radiology, another method of accomplishing approximately the same result was described by Ziedses des Plantes and Cottenot, both employing the term "serioscopy." In this method, several exposures of the subject are made from different angles. The resulting films are then examined in a specially constructed illuminator, in which movement is imparted to the films in such a way that sections of the body radiographed come successively into view. Serioscopy is not exactly identical to body section radiography.

In 1928 Kieffer (6), of Norwich, Connecticut, invented an apparatus for body section radiography which he called an "X-ray focusing machine." He applied for a patent in this country in 1929. Andrews (1) credits him with priority over the investigators mentioned above.

In any method of sectional radiography, the shadows of overlying and underlying structures are displaced, but, because of the penetrability of X-rays, a quantum of these shadows is always present in the resulting film. The greater the dispersion of these shadows, the greater the clarity of the film and the efficiency of the apparatus. Symmetrical or harmonious distribution of unwanted shadows is dependent on the type and extent of movement imparted to tube and film. At the present time there are three mechanically possible methods of securing efficient movement. These are the straight pendulum swing of Vallebona, Chaoul and Grossmann, and the circular and the Archimedean spiral of Ziedses des Plantes. An apparatus of German manufacture modified the pendulum travel in such a way that the path of the X-ray beam follows a sinusoidal curve.

DEFINITION OF TERMS

There are five terms applied to this type of radiography: "stratigraphy," "planigraphy," "tomography," "laminagraphy," and "serioscopy,"[3] the products of these procedures being named, respectively, "stratigraphs," "planigraphs," "tomographs," and "laminagraphs." Serioscopic films have no distinctive appellation. It seems desirable that each of these terms be restricted to the particular apparatus or

[3] Stratigraphy, Vallebona; planigraphy, Ziedses des Plantes; tomography, Chaoul and Grossmann; laminagraphy, Moore; serioscopy, Ziedses des Plantes and Cottenot.

method for which it has been used, and that a general term which is inclusive be applied to all of them. Following the proposal of Andrews, I have urged the use of the term "body section radiography." Ziedses des Plantes has applied the term "analytical roentgenography." Perhaps any general term should include serioscopy, but in the absence of experience I have some doubt as to whether or not it may be considered as being exactly identical to the other procedures.

DESCRIPTION OF THE LAMINAGRAPH

The "X-ray focusing machine" of Kieffer (7) differs from all other types of apparatus, so in justice to other workers I named it the "laminagraph" (9) (figure 1). This apparatus combines all the mechanically possible coördinated movements of tube and film, as far as known, and they can be varied as desired. Certain distinctive points about them should be mentioned. There are seven degrees of amplitude for the circular movement; the spiral is an inverse logarithmic instead of an Archimedean. The laminagraph can approximate the action of the tomograph except that in the former the tube and film move in parallel planes, whereas in the latter the tube moves on an arc. The excursion is the same length in both. In the laminagraph the action can be compounded by combining transverse, circular or spiral travel with the lengthwise excursion. It is possible with this apparatus to carry out easily the serioscopic method, but this has not been attempted. While the thinnest layer that can be radiographed with the laminagraph is from 3 to 5 mm., the thickness of layer can be adjusted at will by altering the extent of movement of tube and film.

The published descriptions of methods and apparatus indicate that claims for superiority of a particular type of apparatus or movement depend on their proponent. Grossmann and Bernard (2) consider that the pendulum action of the tomograph is all that is necessary, at least in chest radiography. Grossmann believes also that the Archimedean spiral is of limited value and only applicable to thin portions of the body. No one has strongly advocated the use of the circular travel of tube and film by any method as yet devised. It is my judgment that this movement is inferior to the other two, but experience with it has been too limited for this to be considered as a final opinion.

In the routine clinical application of the laminagraph, we have used the spiral movement almost exclusively, irrespective of anatomical region or pathological state under investigation. Up to the present

time, this movement has given the optimum thickness of clear layer for the minimum requirement of density differential, and, further, it has dispersed undesired shadows with greater symmetry or evenness. It should be said that pendulum action, such as that of the tomograph, because of its straight-line travel, simplifies greatly the use of a cone at the tube and the Potter-Bucky diaphragm. With combined movements, both methods of diaphragming are difficult, but in the lamina-

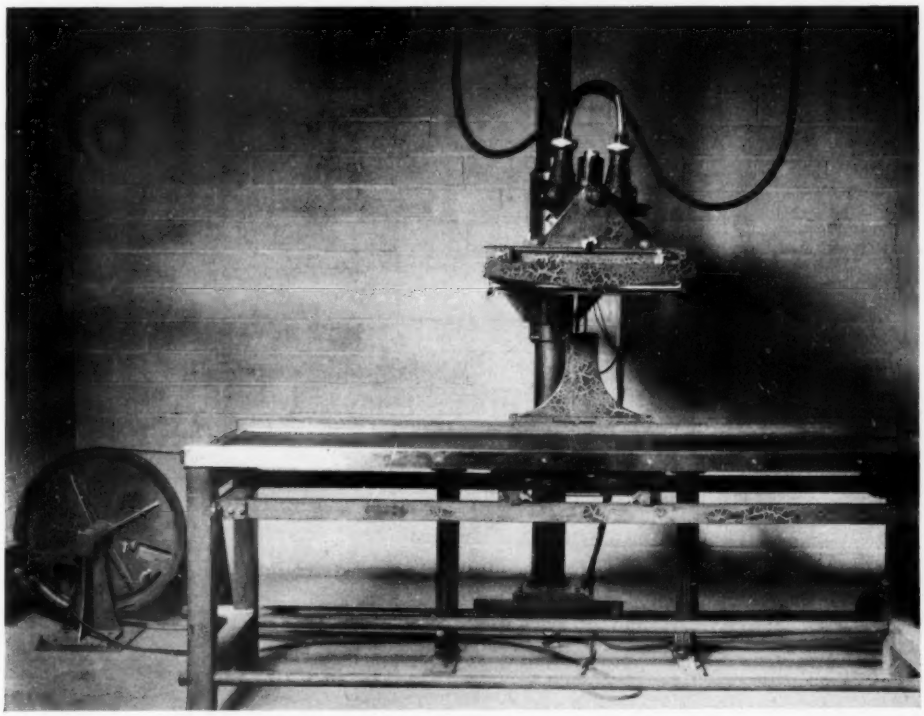

FIG. 1. Photograph of the laminagraph

graph they have been overcome, as the cone effect is secured by the use of slots which move with the tube, and a wafer-type grid that travels with the film carriage. The grid lines are practically obliterated.

CLINICAL APPLICATION OF THE LAMINAGRAPH

Body section radiography has its greatest value in the respiratory and skeletal systems, in the order given, for the obvious reason that in both cases there is a natural density contrast. In those systems in which

there is less density contrast, or where this is brought about by artificial means, the method, to date, has proved of limited use.

The respiratory tract is the anatomical region *par excellence* for any method of body section radiography. In the normal respiratory tract, the air passages, from their remotest upper recesses to the major bronchial divisions, can be delineated easily. The normal larynx with the vocal cords and other component parts has been visualized. With proper technique and serial laminagraphs, the bronchial branches can be followed far out to the very small divisions. Likewise, the vascular tree and its divisions at times can be traced equally as far distally.

The ribs, sternum and dorsal spine can be laminagraphed in either the coronal, sagittal or other planes so that they are freed from the images of superimposed structures. In the case of the upper dorsal spine, even both shoulder girdles can be blurred out in the lateral projection.

Practically nothing has been disclosed, through body section radiography, of the normal diaphragm. This, however, is not the case in pathological conditions to which reference will be made. The foregoing statement holds equally true for the normal mediastinum.

In common with all other X-ray procedures, body section radiography can make neither a bacteriological nor histological diagnosis. However, it can uncover physical conditions in the lower respiratory tract at a stage and with an accuracy which permits a diagnostic conclusion of an exactness hitherto unattainable.

It is a commonplace observation at the autopsy table that large cavities and the true nature of even massive lesions of the lungs proper are discovered, whereas their existence was entirely unsuspected after radiography or other methods of examination (figure 2). Body section radiography probably does not eliminate entirely this contingency but it should go far toward reducing the number of such occurrences.

In early disease of the lungs proper, it is unlikely that this method will be of any great value. It is only when disintegration of lung tissue, infiltration or atelectasis has taken place that there are possibilities. On the other hand, there is ground for hope that early bronchial lesions of an occluding type will be discoverable even beyond the range of the bronchoscope and before atelectasis has occurred. This possibility applies also to nonopaque foreign bodies of smaller size. If atelectasis or infiltration has taken place, termination of the bronchus leading to such an area and dislocation of adjacent bronchi have been demonstrated. (Refer to figure 5.)

In opaque areas in the lungs (figure 3), if disintegration has occurred, cavitations of very small size and their definite location can be found. There is reason to suppose that the absence of cavitation can be shown with as great accuracy as its presence (figure 4). Not only can consolidation, with or without cavitation, and its exact distance from the thoracic wall be found, but also its third dimension, through a suitable number of laminagraphs, can be determined almost exactly.

If there is a total radiographic opacity of the chest, it can be established with a great degree of certainty whether the opacity is due to pleural or pulmonary disease or to a combination of the two. More certain conclusions can be reached if the opacity is due to pulmonary disease than is true if it is confined to the pleurae. If the latter is the case, it can be demonstrated, when properly exposed laminagraphs are made, that the bronchial branches do not extend out so far in the opaque area as they would if the disease were strictly pulmonary. Occasionally there is general total opacity in a standard radiograph where the opacity merges with that of the diaphragm and subdiaphragmatic structures; and on occasion such cases have been shown to be limited pleuropulmonary disease, or localized (encapsulated) pleural disease. In such cases the aerated lung can be demonstrated anteriorly, posteriorly, or laterally, or below the area of opacity. In the last case the diaphragm will be outlined and the true physical nature of the opacity ascertained.

Encapsulated empyema, and its definite limits, at times can be found laminagraphically when otherwise one would be in the dark as to its true nature.

Pyopneumothorax can be discovered when the amount of contained air is too small to be found with standard methods, even with the combined use of overexposure and the rapid Potter-Bucky diaphragm. Bronchial fistulae have been demonstrated in such cases (figure 5).

The laminagraph can contribute greatly in distinguishing pulmonary from pleural disease, or in proving that one is dealing with a combined pleuropulmonary disease (figure 6). Total opacity of a lung, or of a lobe of a lung, for example, one due to a massive neoplastic infiltration, such as that occasionally seen in metastatic sarcoma, should be established as such by the laminagraph. If a total opacity is found in a lung, and it be due to an infectious process with extensive destruction of the lung, with accompanying fibrosis, those portions of destruction which contain even a minimum amount of air can be demonstrated as cavities, and the alternate layers of fibrosis and destruction can be followed

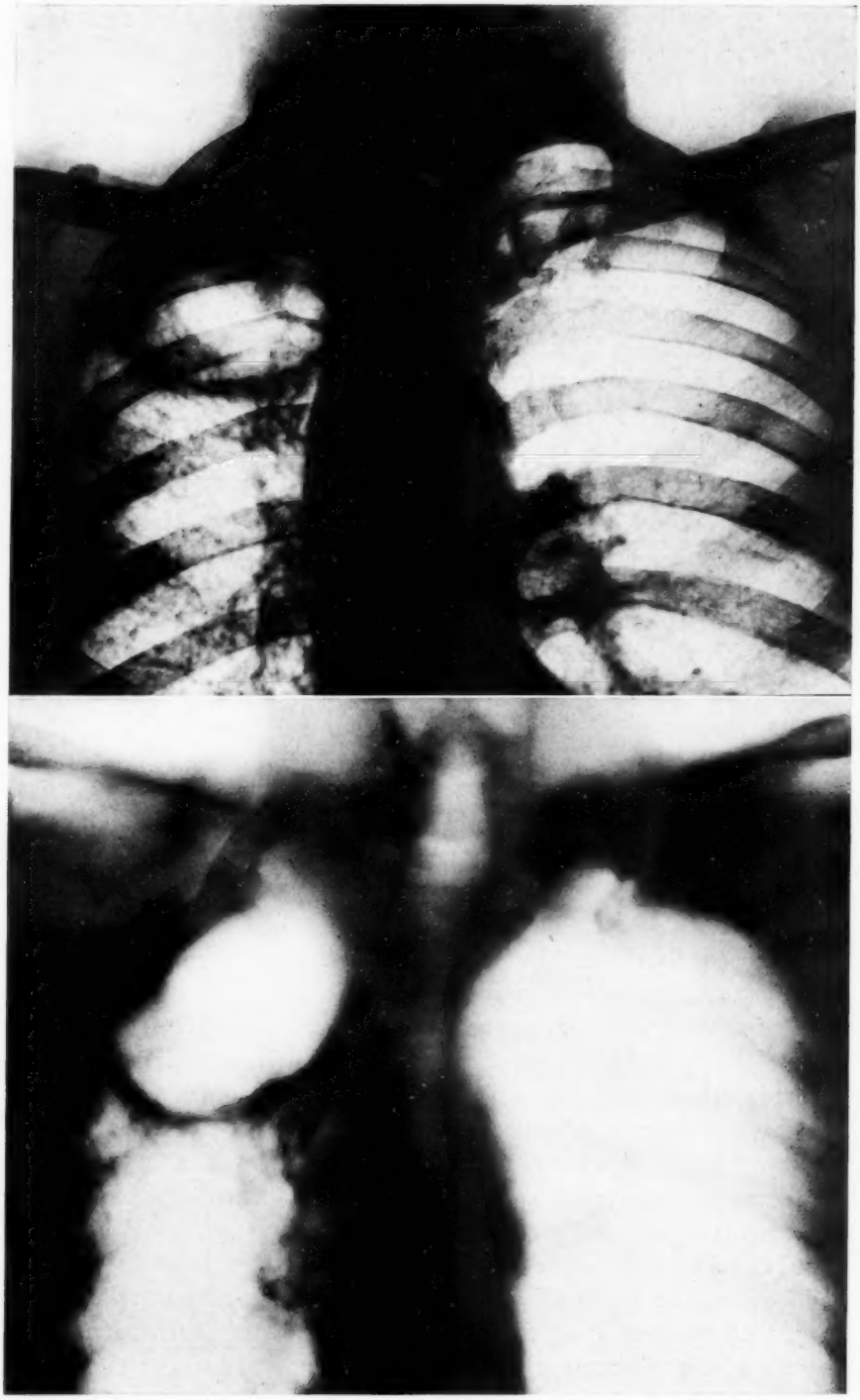

FIG. 2. Pulmonary tuberculosis. Above, conventional radiograph suggests presence of cavity in right apex. Below, laminagraph reveals its immense size.

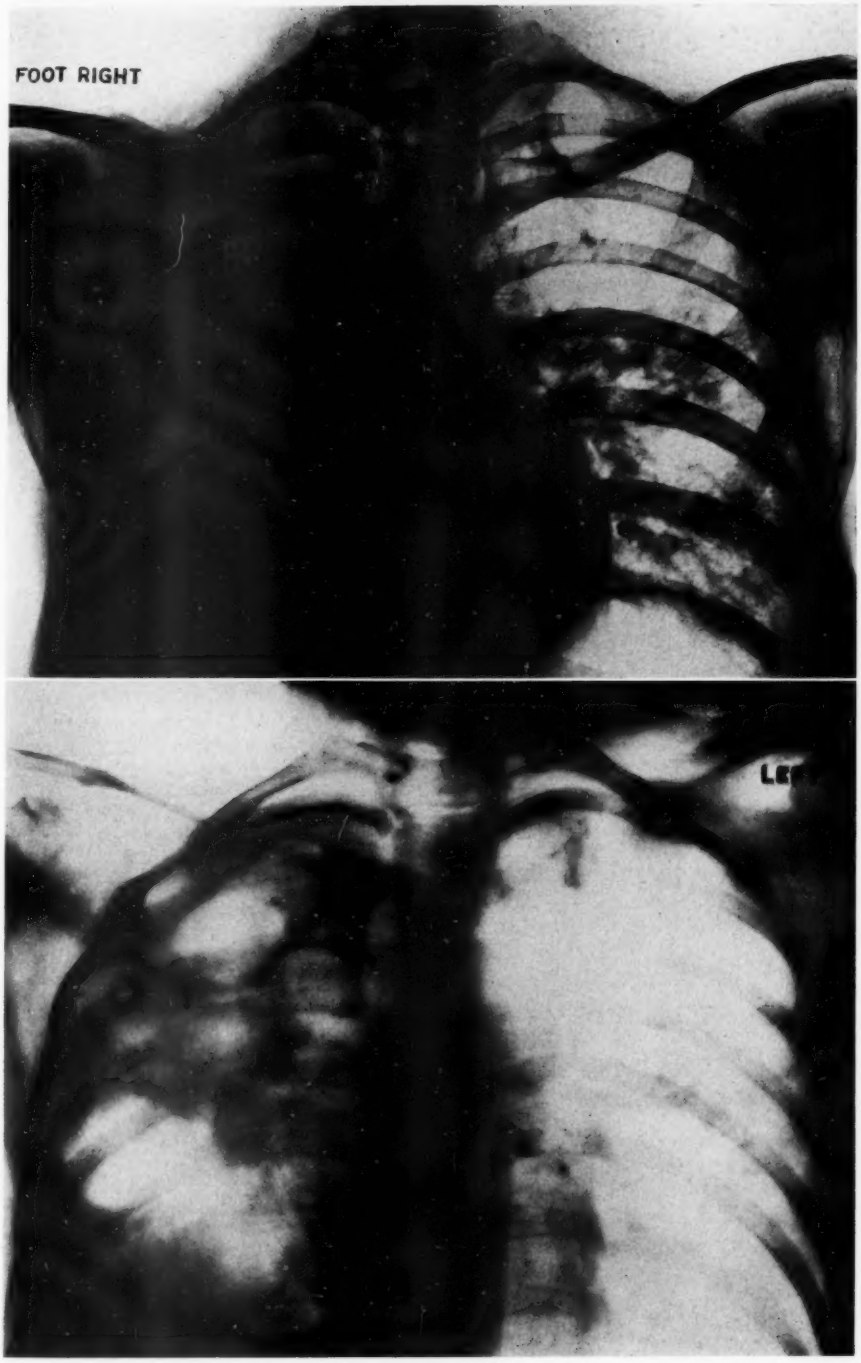

FIG. 3. Pulmonary tuberculosis. Above, standard film. Below, laminagraph reveals multiple cavitation in opaque area.

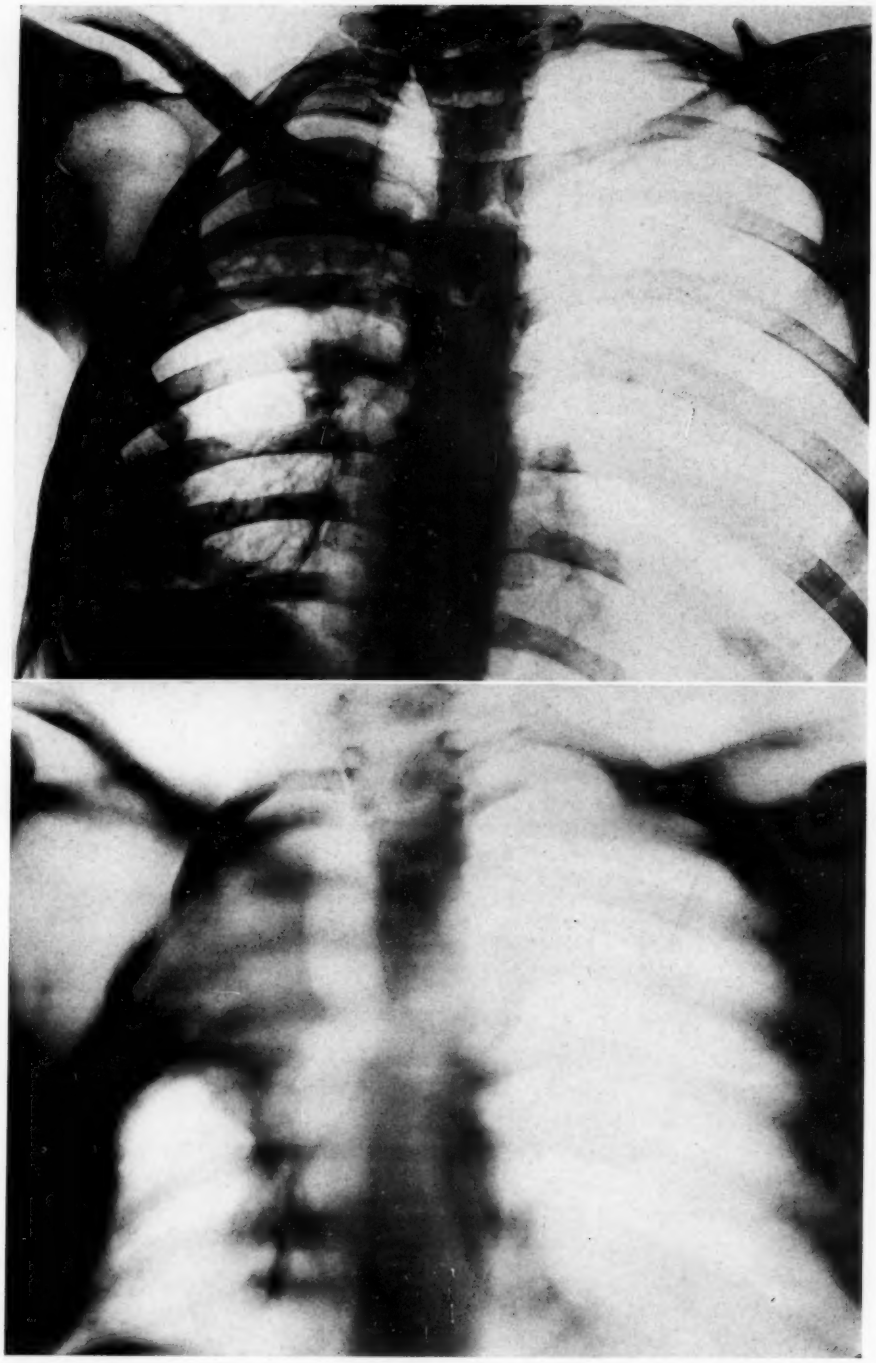

FIG. 4. Pulmonary tuberculosis. Above, conventional film. Below, laminagraph reveals consolidation of apex of right lung and absence of cavitation.

FIG. 5. Old empyema. Above, cavity suggested in standard film. Below, laminagraph of same illustrates combination of pleural and pulmonary disease. Note multiple bronchial fistulae.

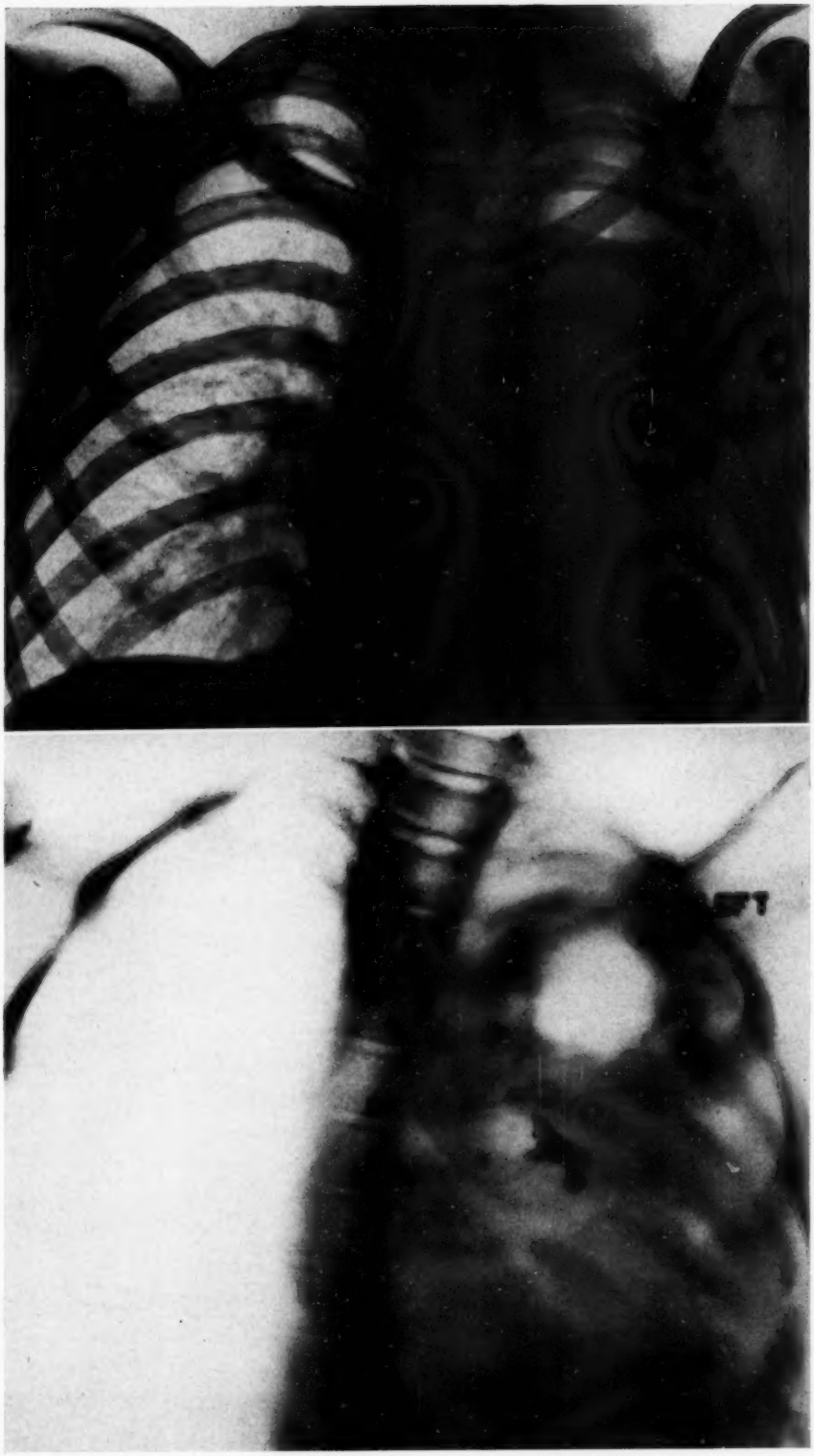

FIG. 6. Above, standard film of chest in erect position, thought to be pyopneumothorax. Below, laminagraph reveals presence of lung abscess.

throughout the involved area. Bronchiectasis and cystic disease (whatever its aetiology) can be found with equal certainty.

It follows from this that the location, size and physical characteristics of pulmonary cavities can be known accurately. If the disease is one requiring external drainage, the surgeon can plan his approach with the greatest assurance and will know in advance whether there is a single cavity or multiple cavitation, the thickness of the walls of the cavity, and whether it is multilocular or septate. It is well known that prognosis becomes more unfavorable with the number of attempts at drainage of a pulmonary abscess. With their location definitely ascertained by the laminagraph, it should be possible to drain all existing pockets at one operation. In pulmonary cavitation unsuitable for treatment by external drainage, the type, method and extent of collapse therapy to be employed can be established, by body section radiography, with an assurance beyond that of any other means of examination (figures 7, 8, 9 and 10).

A few words in regard to the laminagraphic examination of the mediastinum. Tumors, abscesses and aneurysms, which in a standard examination are obscured by overlying structures, have been shown and located by means of laminagraphy. Dislocations and compressions of the tracheobranchial tree and dislocations of the great vessels have been laminagraphed successfully. In one case a tracheo-oesophageal fistula was visualized clearly because of the connecting air column.

As this presentation is before the National Tuberculosis Association, some reference should be made to the use of body section radiography in tuberculosis of anatomical regions other than the chest. This method of examination has been invaluable in the study of tuberculosis of the vertebrae. It gives far more precise information as to the extent of the disease than possibly can be gained from standard X-ray procedures. This is true particularly of the dorsal vertebrae in the lateral projection. Low cervical or high dorsal vertebral tuberculosis can be delineated clearly through the shoulder girdles.

Tuberculosis of the joints of the extremities as yet has not been examined with the laminagraph, but there are possibilities of value in selected cases. It should be mentioned in passing that bone tuberculosis can be laminagraphed successfully through plaster casts or through any other retentive apparatus of like opacity.

In tuberculosis of the intraäbdominal organs, there is little to be anticipated unless, or until, calcification has occurred. If calcification

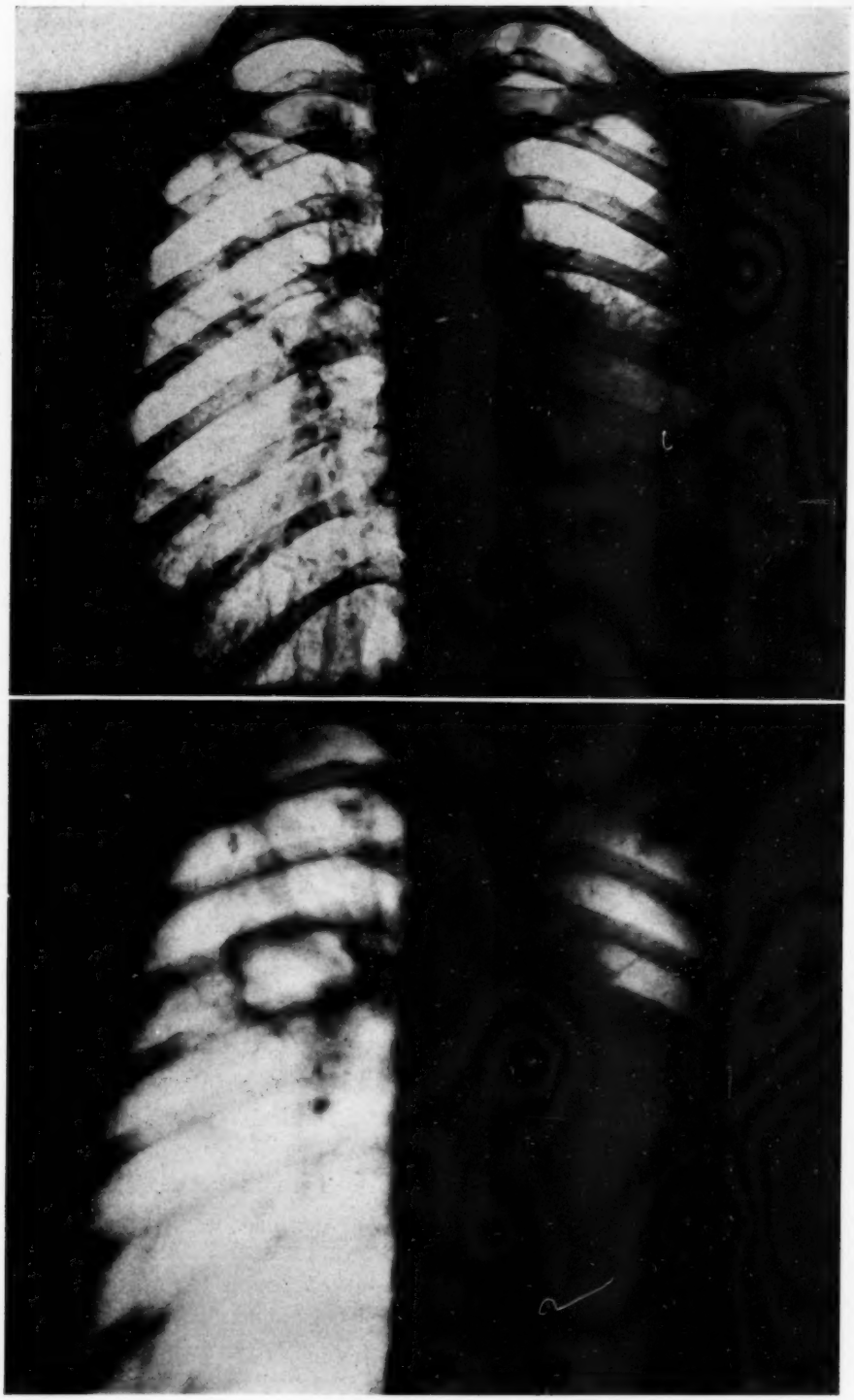

FIG. 7. Above, pulmonary tuberculosis involving chiefly left side; left phrenicectomy; suggestion of cavity of right lung. Below, laminagraph discloses right perihilar cavity.

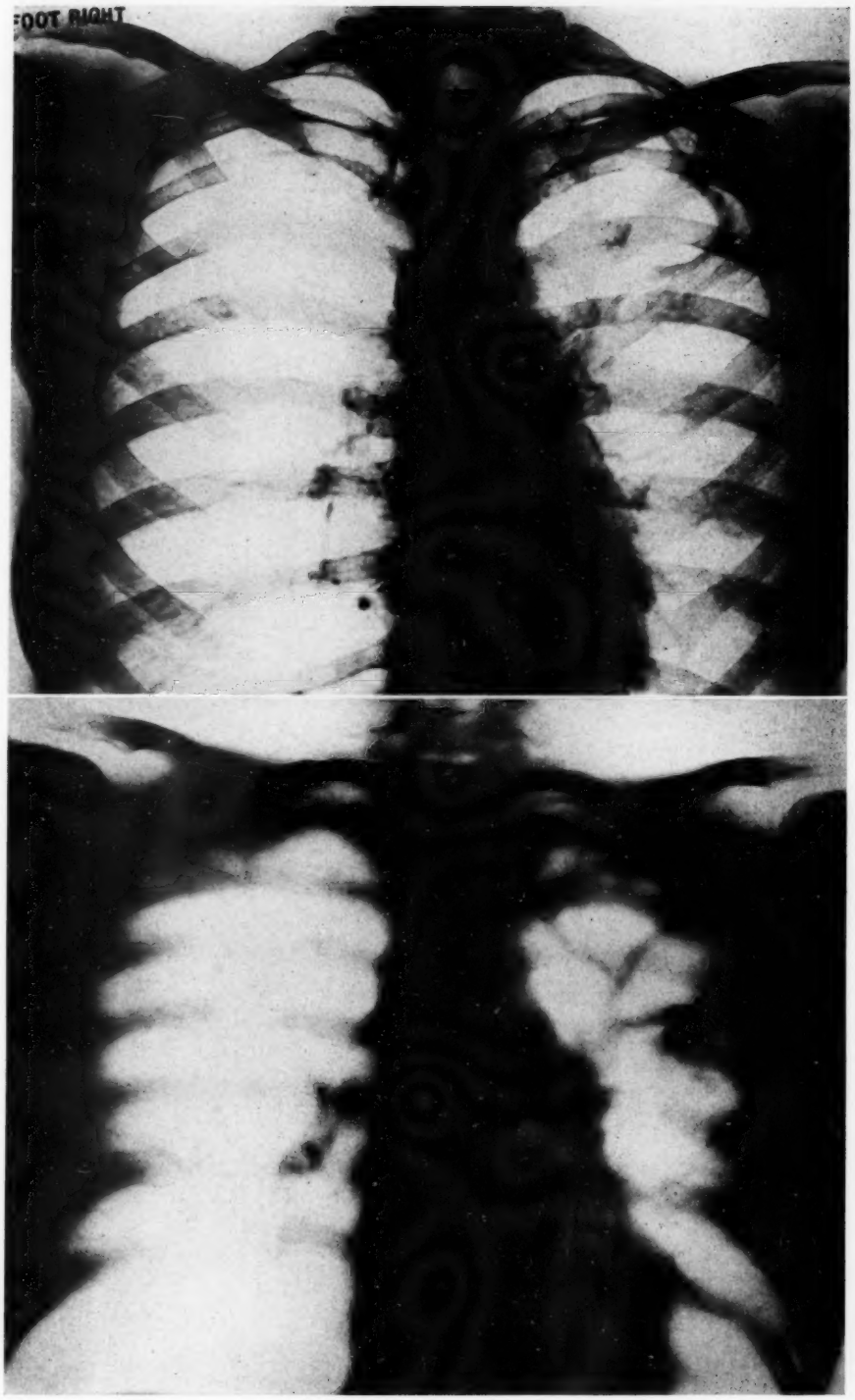

FIG. 8. Pulmonary tuberculosis. Above, conventional film suggests cavity at left apex. Below, laminagraph reveals multiple or multilocular or septate cavitation.

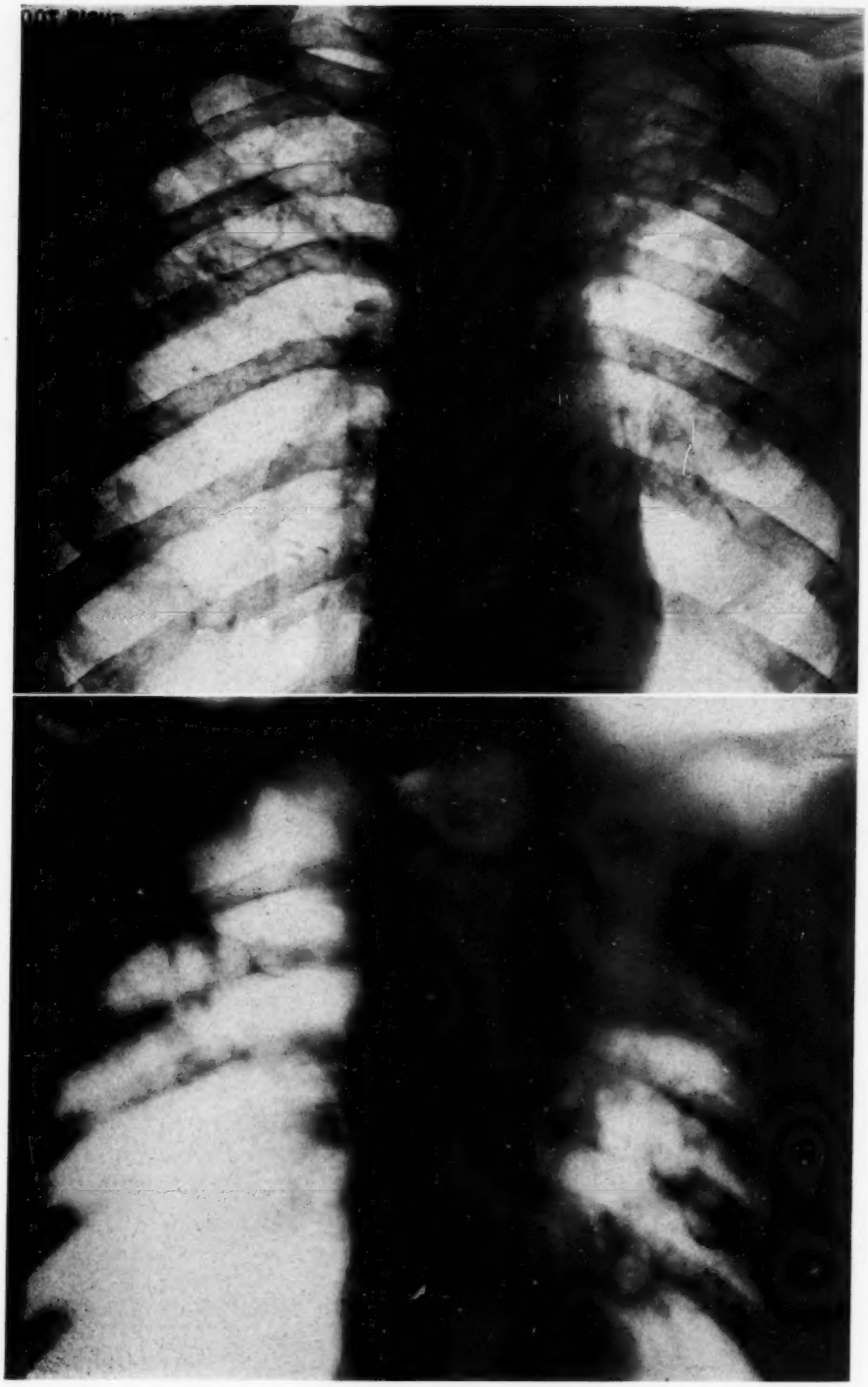

FIG. 9. Pulmonary tuberculosis. Above, conventional radiograph; note cavitation in right apex. Below, laminagraph reveals additional unsuspected small cavitation in the midsection of opposite lung.

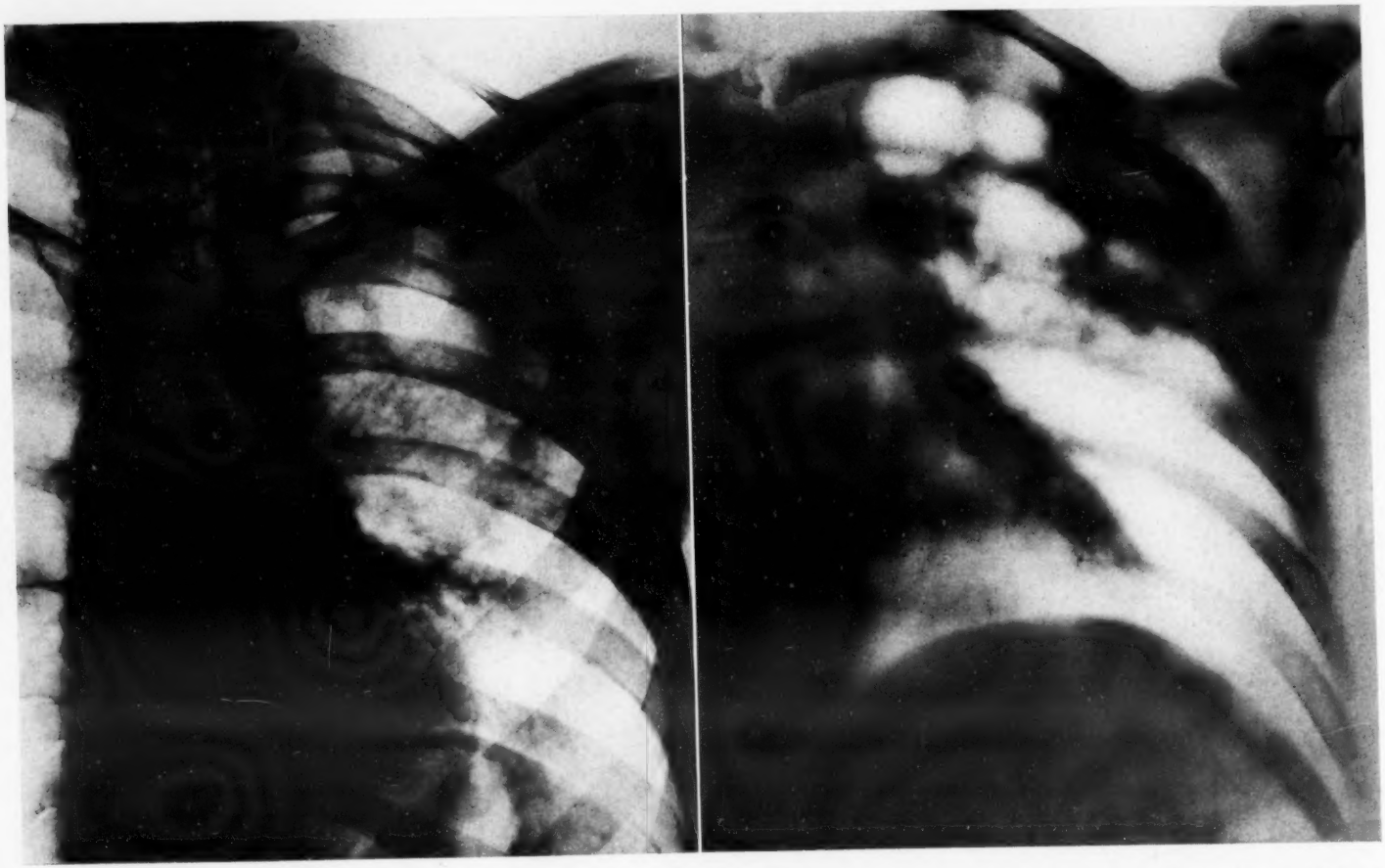

FIG. 10. Pulmonary tuberculosis. Left, conventional radiography shows cavity in left apex. Right, laminagraph discloses three additional separate cavities.

is present in even a slight degree in other soft tissues of the body, then aid might be had from the laminagraphic examination of tuberculosis in such tissues.

TECHNIQUE

Something should be said in regard to the standard radiographic technique before discussing that used in laminagraphy. The latter should not be resorted to until symptoms and objective findings by standard methods are not in accord.

Pulmonary cavitation often can be shown, when it is not found with a standard film, by underexposure or, more important, overexposure, especially if a fast-moving Potter-Bucky diaphragm is employed. In the case of massive lesions in the lungs, it is probable that in the future fluoroscopy, as a preliminary to laminagraphy, will supplant conventional films, stereoscopic or otherwise, and will, therefore, simplify and make less laborious the laminagraphic examination. Bronchography still will have its field of usefulness whether laminagraphs are used or not.

In body section radiography, rapidity of exposure must of necessity be less than is the case in the standard examination. In the tomograph, Chaoul and Grossmann, and McDougall (8) have reduced the time to one second and consider this speed adequate. Exposures of this duration can be made with the laminagraph, but we have found that longer exposures have been superior. The element of time in exposure is dependent on how the apparatus is powered. The greater this is, the faster the exposure can be made, up to that point where the inertia of the heavy moving parts cannot be overcome. It is unlikely that this time element ever will be less than one second.

Exposure time is a factor of current used, so the consideration of current in body section radiography requires no special statement.

The voltage necessary is the same in standard and in body section radiography.

Target-film distance is set by the ratio of the grid used.

The number of exposures to be made in body section radiography is determined as the examination progresses. Chaoul and Grossmann, McDougall,[4] and Cottenot advocate three exposures, one at the coronal plane, and one each half-way dorsally and ventrally. We have found that it is desirable, if not mandatory, to make a larger number of sections,

[4] Everyone interested should read the excellent articles of Chaoul, Grossmann and McDougall.

the usual practice being to make one at every one centimetre interval throughout the suspected area. If a lesion is very large, the number of layers and, therefore, the number of films used is correspondingly reduced. In some regions and in some conditions only one exposure is necessary, notably in the case of the lateral view of the dorsal spine. As has been mentioned above, serial laminagraphs can give almost exactly the third dimension in the case of a cavity or area of consolidation.

Positioning of the patient follows conventional lines. In all methods, except in Vallebona's stratigraph and the Siemens planigraph, the patient is in the recumbent position. Many feel that the horizontal position is a handicap, chiefly because fluid levels may escape detection. I cannot subscribe to this view because supernatant air in a cavity, if present even in a small quantity, should be demonstrable by serial laminagraphs. The established principle that the part under investigation should be as close to the film as possible will determine, in the case of the chest, whether the patient should be in the prone or supine position.

It should not be anticipated that body section radiographs will have the photographic beauty of conventional films. This is because of the fact that, as was pointed out in the beginning of this paper, a portion of the dispersed shadows always remains to blur and make obscure the resulting film. It is also necessary in the technique of laminagraphy, under certain conditions, to over- or underexpose film in order to develop properly the difference in density.

SUMMARY

1. Body section radiography has been defined and its methods and apparatus described.

2. An attempt has been made to analyze and evaluate the possibilities inherent in this type of radiographic examination.

3. Emphasis has been placed on the employment of body section radiography in diagnosis and treatment of pulmonary disease, both tuberculous and nontuberculous.

4. Brief reference has been made to the use of this method in extrapulmonary tuberculosis.

5. It is believed that the type of apparatus which has been employed is superior to others.

CONCLUSIONS

Since body section radiography can discover pulmonary cavitation with such accuracy and at such an early stage, it certainly promises to be invaluable in the diagnosis, treatment, prognosis and management of the tuberculous patient. It is invaluable in the diagnosis and treatment of intrathoracic suppurative disease and should be of the greatest aid to the operating surgeon. It will be of help in other chest diseases. It has a definite place in tuberculosis and other diseases of the skeleton.

Grateful acknowledgment is made to Professor Evarts A. Graham and to Dr. Brian Blades for invaluable help and coöperation, and permission to exhibit material from their service at the Washington University School of Medicine, St. Louis.

There is a fairly extensive literature on the subject of this paper. As this is complex, scattered, and at times controversial, the writer has done his best to make proper acknowledgment to all who have contributed to the development of body section radiography, irrespective of type of apparatus or method employed. If the work of anyone has been overlooked it was unintentional.

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MEDIASTINAL AND HILAR ANGIOGRAPHY IN PULMONARY DISEASE[1,2]

A Preliminary Report

ISRAEL STEINBERG AND GEORGE P. ROBB

Visualization of the blood vessels of the mediastinum and the hilum is now a practical procedure. In the past, Carvalho and his coworkers (1) and others (2) opacified the pulmonary artery and its branches by catheterization of the heart and the injection of a concentrated solution of sodium iodide. Introduction of the contrast substance directly into the heart in this way prevents visualization of the superior vena cava and its tributaries, and their method also fails to outline the left side of the heart and the aorta. The difficult nature of the technique, moreover, has restricted its clinical use. During the past year, Castellanos, Pereiras and Garcia outlined the right chambers of the heart and the pulmonary artery in young children by intravenous injection but were unable to visualize the left side of the heart and the aorta.

We have recently developed a method for the visualization of the superior vena cava, the chambers of the heart, the pulmonary circulation and the aorta in man (4), thereby completing contrast roentgenography of the thoracic structures. Heretofore only visualization of the bronchi by the use of lipiodol, of the oesophagus by barium, and of the lung and pleura by pneumothorax have been practical.

Our method consists of the rapid injection of the organic iodide compound diodrast (5) (3, 5, diïodo-4-pyridone-N- acetic acid and diethanolamine) into the cephalic or basilic vein of the arm and the taking of roentgenograms at appropriate intervals. We have used a 70 per cent solution as a rule, the dosage for pulmonary arteriography in the average adult being from 25 to 35 cc. The duration of injection should not exceed two seconds. A detailed description of the technique has been reported previously (4).

[1] Presented at the Joint Medical Sessions of the Pathological and Clinical Sections at the 34th annual meeting of the National Tuberculosis Association, Los Angeles, California, June 21, 1938.

[2] From the Department of Therapeutics, New York University College of Medicine, and the Tuberculosis Service of Bellevue Hospital, New York City.

No serious consequences have followed 238 injections in 127 patients, of whom 42 were normal, 47 had pulmonary disease, and the remainder heart disease. We have studied the following pulmonary disorders, in many instances making repeated observations in the posteroanterior and the two oblique positions and once in the lateral: pulmonary tuberculosis, 13 cases; silico-tuberculosis, 1; resolving pneumococcic pneumonia, 1; lung abscess, 3; bronchiectasis, 11; pulmonary fibrosis and emphysema, 6; silicosis, 1; primary carcinoma of the bronchus, 4; metastatic carcinoma, 1; mediastinal tumor, 4; leukaemic infiltration of the lung, 1; and pulmonary cyst, 1. There has been no evidence of iodism, or activation or aggravation of pulmonary disease.

Excellent filling of the basilic or cephalic, axillary, subclavian, and innominate veins, and the superior vena cava, as well as the right auricle, can be secured in from one to one and one-half seconds after the beginning of the injection in the average subject. The right ventricle and the pulmonary artery and its branches can be outlined in from three to five seconds, whereas the pulmonary veins, the left auricle, the left ventricle and the aorta require a longer interval (4, 6). Satisfactory pyelograms and even nephrograms may be obtained because of the large dosage of diodrast.

X-RAY TECHNIQUE

The film is taken in the customary posteroanterior position because the anteroposterior and supine positions give less contrast and detail. The subject is seated with the arms extended upward and outward to facilitate injection. The apices are obscured in this position because of the elevation of the clavicles and scapulae but this may be overcome in part by increasing the kv. p. Recently we have eliminated the difficulty by the use of an adapter which permits injection in the routine position.

Our preliminary studies were made with 50 milliamperes exposure. Subsequently we have used an exposure of 300 milliamperes, a distance of 72 inches and a duration of exposure of one-twentieth second. The kv. p. for the control film has varied with weight and build. For the contrast film it has been necessary to increase it by 4 to 6 kv. p. as in bronchography. For example in case 5 (figure 11), the weight of the patient was 115 lbs., the kv. p. was 68, whereas for the contrast film (figures 12 and 13) the kv. p. was 73. An exposure of one-twentieth of a second or less is necessary to lessen the blurring which is produced by motion of the pulmonary blood vessels. For this reason synchroniza-

tion of exposure and heart beat is desirable. Two exposures per injection have been possible by the use of a stereoscopic casette shifter. We have used a tube of medium focus which is centred at the level of the scapular spine. The injector is protected from radiation by the use of a lead screen.

The Lysholm grid has been of value in outlining vascular structures in patients with extensive pulmonary disease (figures 6 to 10). Used with the standard casette shifter, this grid permits two exposures per injection, whereas the fast moving Potter-Bucky screen allows only one.

Frequent roentgenograms are desirable since they would give a complete picture of the structures outlined progressively from the point of injection and would thus obviate the need for further study in that position. Cineradiography or rapid film shifting offer probable solutions. Further economy could be secured by the taking of films simultaneously in the posteroanterior and the lateral, or the two oblique positions.

CASE REPORTS

The following case reports illustrate the type of information which mediastinal and hilar angiography offer in pulmonary disease.

Case 1: Substernal goitre; occlusion of left innominate vein; stenosis of right innominate vein; collateral circulation. A 63 year old Irish-American laborer was found in 1929 to have a substernal adenoma of the thyroid gland which could not be removed. The goitre became markedly increased in size, especially to the left in 1935, causing paralysis of the phrenic and recurrent nerves. Because of the presence of cyanosis and collateral circulation from the upper extremities, a clinical diagnosis of obstruction of the superior vena cava was made. Radiation therapy produced a decrease in the size of the tumor but the collateral circulation, cyanosis and paralysis of the nerves persisted. Figure 1 shows the collateral circulation from the left arm. The film was taken seven seconds after the beginning of injection and reveals many tortuous veins extending downward over the left shoulder and thorax. On stereoscopy most of them were found to course anteriorly along the ribs and some even crossed to the opposite side. The left innominate vein failed to fill, indicating the site of obstruction. Subsequent injections in the right arm (figure 2) showed slight stenosis and displacement of the right innominate vein, with the convexity conforming to the goitre, while the superior vena cava was entirely patent. There was only a minor degree of collateral circulation shown in a later film. The elevation of the left diaphragm due to paralysis and the triangular superior mediastinal mass with narrowing and deviation of the trachea typical of substernal goitre may be seen.

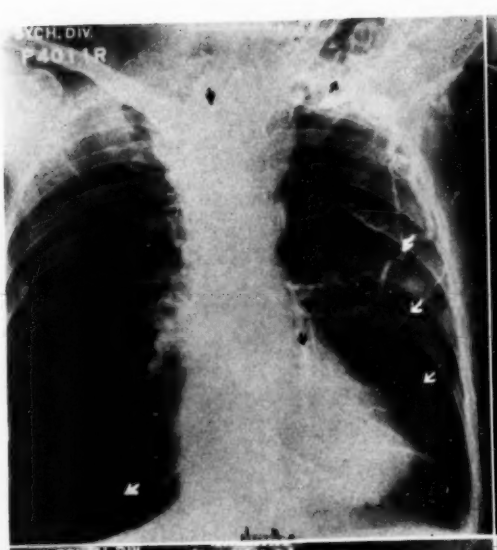

FIG. 1

FIG. 2

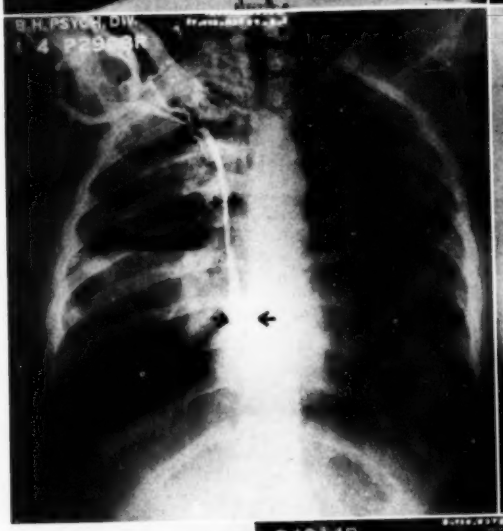

FIG. 3

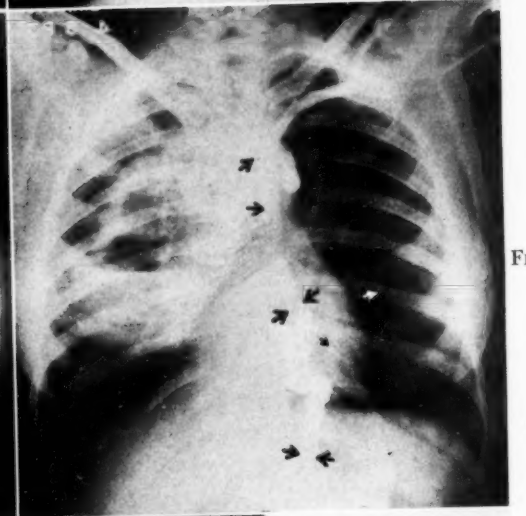

FIG. 4

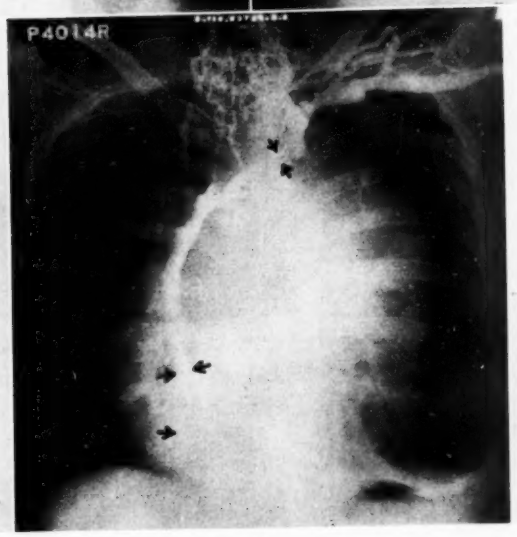

FIG. 5

Case 2: Mediastinal Hodgkin's disease and lung abscess; stenosis of right innominate vein; occlusion of left innominate vein; collateral circulation, left azygos system. A 17 year old female developed symptoms of mediastinal pressure in 1934 but the diagnosis of Hodgkin's disease was not made until 1936 when a biopsy was secured. Improvement followed radiation therapy at that time but in July, 1937, a lung abscess developed in the right upper lobe. Figure 3, taken one and one-half seconds after injection, reveals extreme stenosis of the right innominate vein with but little collateral circulation. The superior vena cava is markedly narrowed and displaced toward the right, and can be seen emptying into the right auricle which is beginning to fill. The enormous abscess with fluid level is visible in the right upper lung field. Figure 4, taken at three seconds, shows the collateral circulation discovered by injections of the left side. The cephalic, axillary, and subclavian veins are filled, whereas the left innominate vein cannot be found. In its place there is a coiled structure which courses caudally as a tortuous, dilated vessel having intercostal communications, to disappear below the diaphragm. Stereoscopic examination shows that this vein lies posteriorly and adjacent to the left border of the spine, and therefore must be part of the azygos system. The next film, taken at five seconds, showed filling of the right side of the heart and pulmonary artery, thus establishing the communication of the azygos system with the inferior vena cava. Looking back to figure 3, in which the left hemithorax is free from diodrast, the azygos system can now be recognized, although it was impossible before.

Case 3: Mediastinal tumor; stenosis of left innominate vein; collateral circulation; displacement of superior vena cava; localization of right auricle. A 36 year old male first noticed dyspnoea during an acute upper respiratory infection. Chest films reveal a huge lobulated tumor which fills the anterior mediastinum and occupies two-thirds of the transverse diameter of the chest as shown in figure 5. Since radiation therapy has failed to reduce the mass, surgical ex-

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FIG. 1. Case 1. (7 seconds) Substernal goitre. Occlusion of the left innominate vein. Collateral circulation left shoulder and thorax. Note collaterals in lower right chest.

FIG. 2. Case 1. (1½ seconds) Substernal goitre with deviation of the trachea. Stenosis of the right innominate vein. Elevation of the left diaphragm (phrenic nerve paralysis).

FIG. 3. Case 2. (1½ seconds) Mediastinal Hodgkin's disease. Lung abscess, right upper lung field. Stenosis right innominate vein. Collateral circulation right shoulder and thorax. Superior vena cava normal and displaced. Right auricle filled. Note indistinct shadow of left azygos system.

FIG. 4. Case 2. (3 seconds) Mediastinal Hodgkin's disease. Occlusion of left innominate vein. Azygos system indicated by black arrows. Note its disappearance below diaphragm.

FIG. 5. Case 3. (2 seconds) Mediastinal tumor. Stenosis left innominate vein. Collateral circulation. Right auricle located.

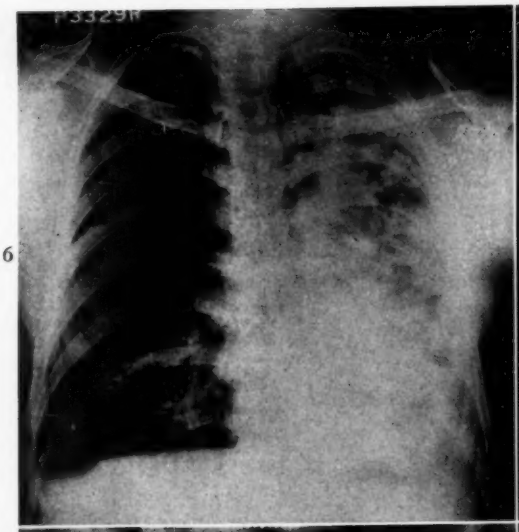

FIG. 6

FIG. 7

FIG. 8

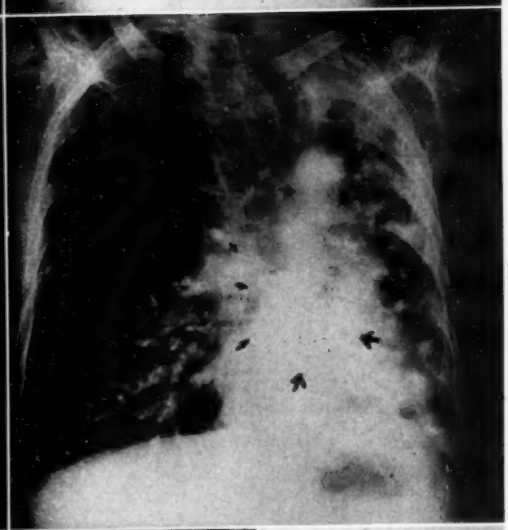

FIG. 9

FIG. 10

ploration, for diagnosis and, if possible, extirpation, is planned. Figure 5, taken two seconds after injection into the left cephalic vein, shows good filling to the left innominate vein. At this point the vessel becomes narrowed and irregular, producing an extensive collateral circulation in the cervical region. The superior vena cava is markedly bowed toward the right and can be seen entering the right auricle, thus localizing the position of the heart, which previously had been impossible.

Case 4: Fibrothorax; localization of superior vena cava, cardiac chambers, pulmonary artery, right pulmonary circulation and aorta. A 49 year old laborer has had acquired saccular bronchiectasis and fibrosis of the entire left lung for many years, causing displacement of the heart, trachea and mediastinum. In the control film (figure 6) the extensive pulmonary disease prevents recognition of the heart and the aorta. The contrast film (figure 7), made with a Lysholm grid two and a half seconds after injection, shows the left innominate vein to be kinked and displaced to the left. The superior vena cava and the right auricle are well filled and lie to the left of the spine. The right ventricle and pulmonary artery are beginning to fill but are better seen in figure 8, taken at four seconds. In this film, displacement of the faintly outlined right innominate vein and superior vena cava can be seen. The right auricle and ventricle, and the pulmonary artery appear in profile as in the right anterior oblique position, indicating that the heart has been rotated toward the left. The right pulmonary arterial tree is well outlined; the left cannot be seen. The right pulmonary veins are well filled in figure 9, taken at seven seconds. The left auricle, the left ventricle and the ascending aorta are opaque although ill defined, thus completing the localization of the heart and great vessels. Figure 10, at eight and one-half seconds, gives a clearer picture of the left ventricle and the entire thoracic aorta.

Case 5: Mediastinal and hilar tuberculosis; distortion of superior vena cava; failure of visualization of right pulmonary arterial tree. A 20 year old Negro

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FIG. 6. Case 4. Control. Fibrothorax. Extensive fibrosis and excavation, left hemithorax with deviation of the trachea and mediastinum. Heart completely drawn into left thorax and contours obscured.

FIG. 7. Case 4. (2½ seconds) Fibrothorax. Kinking left innominate vein. Displacement superior vena cava. Right auricle and ventricle filled.

FIG. 8. Case 4. (4 seconds) Fibrothorax. Left innominate vein faintly outlined. Right auricle, ventricle and pulmonary artery opaque. Left pulmonary artery unrecognized.

FIG. 9. Case 4. (7 seconds) Fibrothorax. Right pulmonary veins, left auricle and aorta opaque.

FIG. 10. Case 4. (8½ seconds) Fibrothorax. Left ventricle and entire thoracic aorta outlined.

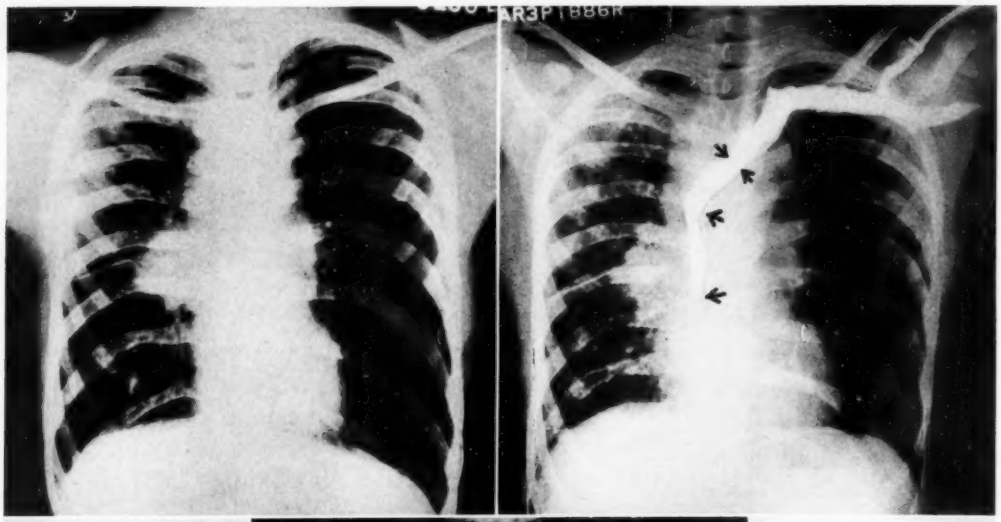

FIG. 11

FIG. 12

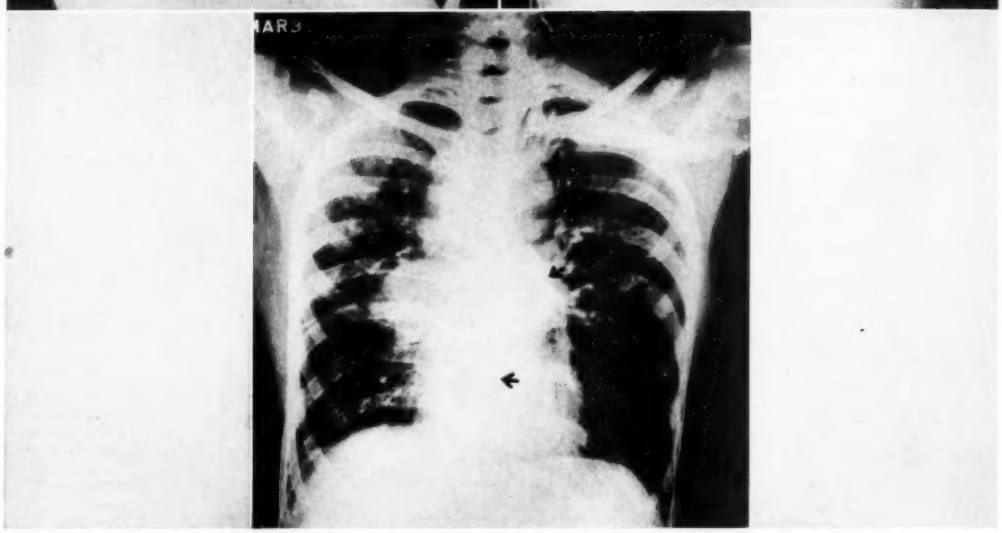

FIG. 13

FIG. 11. Case 5. Control. Right hilar and mediastinal adenopathy. Tuberculous infiltration right upper lung field.

FIG. 12. Case 5. (1 second) Mediastinal and hilar tuberculosis. Left cephalic, axillary, subclavian and innominate veins filled. Regurgitation into basilic vein. Superior vena cava distorted. Auricle beginning to fill.

FIG. 13. Case 5. (3 seconds) Mediastinal and hilar tuberculosis. Visualization right auricle, ventricle, pulmonary conus and artery. Interventricular septum. No opacification of right pulmonary circulation.

boy was recently found to have tuberculosis of the mediastinal and right hilar lymph nodes as well as tuberculous infiltrations of the right upper lung field (figure 11). He had episodes of wheezing, denoting pressure on the tracheobronchial structures. The contrast film (figure 12), taken one second after the beginning of injection, shows the irregularity of the superior vena cava, evidently caused by enlarged nodes. The right auricle is just beginning to fill. At three seconds (figure 13), the right side of the heart is opaque and the location of the interventricular septum can be made out. The pulmonary artery is displaced to the left, causing prominence of that hilar region which had been erroneously ascribed to adenopathy. The glandular mass above can be easily differentiated from the pulmonary artery. The blood vessels to the left lung appear normal in contrast to the right side in which there is little or no filling.

Case 6: Bronchiectasis and pulmonary fibrosis; rotation and displacement of heart and pulmonary artery; absence of visualization of arteries to left lower lobe. A 62 year old white man shows calcification of the left pleura, circular excavations and fibrosis of the left lower lung field, thickening of the costophrenic pleura, and adhesions causing the heart to be drawn to the left (figure 14, control film). A bronchogram revealed saccular bronchiectasis of the left lower lobe. The contrast film (figure 15), taken at three seconds, shows the pulmonary artery pulled over and rotated to the left, thereby bringing its right division forward and the left posteriorly. This explains the prominence of the right arterial tree in the posteroanterior position. There is less opacification of the left upper lobe and none of the lower. In the left anterior oblique position (figure 16), at three seconds, the right auricle and ventricle are filled and the right pulmonary artery and its branches are well defined. The left pulmonary artery, however, appears dwarfed, the usual large trunk to the lower lobe being reduced to a single branch. Figure 17 shows the same subject in the right anterior oblique position. The superior vena cava leads into the right auricle, the right ventricle is filled, and the pulmonary valve, sinuses and artery are visible. Again there is the poor filling of the left pulmonary arterial tree, particularly to the lower lobe.

Case 7: Chronic bronchitis, pulmonary fibrosis and emphysema; enlargement of right ventricle, pulmonary conus and pulmonary artery. A 57 year old laborer who had suffered from chronic bronchitis for years has a barrel chest, expiratory wheezing and markedly diminished breath sounds. The contrast film, figure 18, taken six seconds after injection, shows enlargement of the pulmonary conus, the pulmonary artery and the branch to the right lower lobe. The heart also is enlarged to the right.

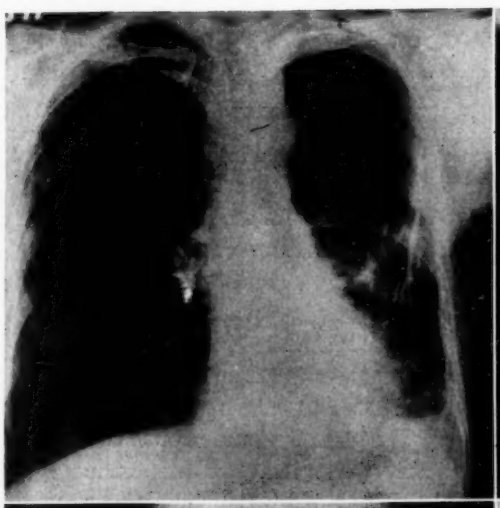

FIG. 14

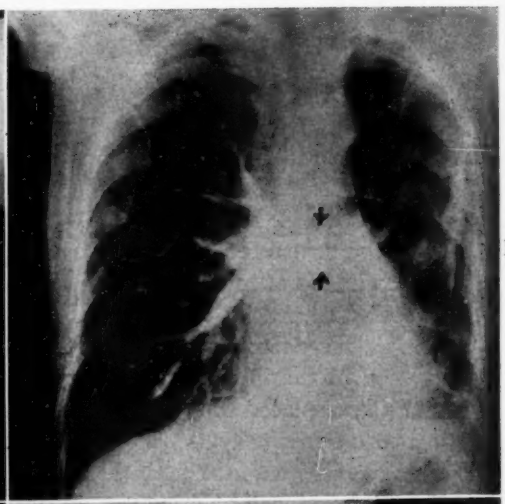

FIG. 1

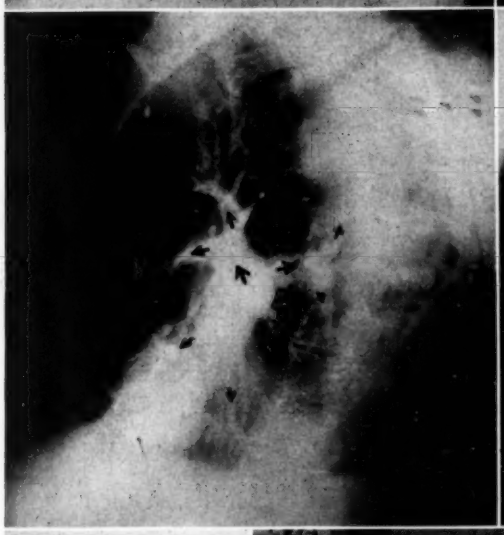

FIG. 16

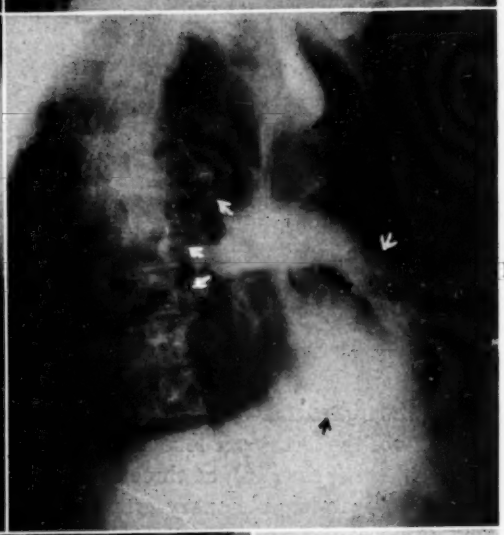

FIG. 1

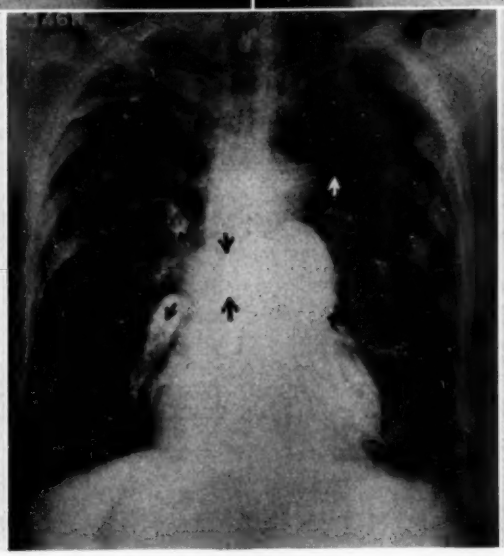

FIG. 18

DISCUSSION

The vascular nature of the hilum and characteristic deviations from normal have been demonstrated by Carvalho and his group (1) and others (2). Precise information concerning the vascular components of the mediastinum, however, has not been obtainable. We have been able to outline the superior vena cava and its tributary veins, the cavities of the heart, the pulmonary veins and the aorta, as well as the pulmonary arterial tree. Visualization in the oblique and lateral positions, in addition to the posteroanterior view, has given a more complete picture of these structures and their relationship in normal and diseased conditions.

It has been possible to identify the site of stenosis or occlusion of the innominate vein and to demonstrate the collateral circulation. In the patient with substernal goitre, the superior vena cava was patent, contrary to earlier impression, and there was moderate stenosis of the right, and occlusion of the left innominate vein. Now that the site of obstruction has been found, it seems evident that it should have been suspected because of the greater extent of the tumor to the left and the paralysis of the recurrent and phrenic nerves. The patient with Hodgkin's disease (case 2) exhibits two types of collateral circulation from the upper extremities; the usual one on the right involving the veins of the shoulder girdle and thorax; and the azygos system on the left, not demonstrable before during life. The prompt arrival of diodrast in the pulmonary circulation proves the efficiency of this route. Another example of collateral circulation is seen in the patient with mediastinal tumor, in which the cervical vessels played the major rôle. The kinking of the left innominate vein, without obstruction, in accommodation to the changes caused by fibrothorax is shown in figure 7.

FIG. 14. Case 6. Control. Bronchiectasis and fibrosis. Calcification of left pleura. Fibrosis and small excavation left lower lung field. Displacement of the heart by adhesions.

FIG. 15. Case 6. (3 seconds) Bronchiectasis and fibrosis. Opacification of right pulmonary arterial tree and left upper lung field. None in lower.

FIG. 16. Case 6. (3 seconds) Bronchiectasis and fibrosis. Left anterior oblique position. Right ventricle and pulmonary artery filled. Branches to the right filled. Left pulmonary artery dwarfed.

FIG. 17. Case 6. (3 seconds) Bronchiectasis and fibrosis. Right anterior oblique position. Superior vena cava, right auricle and ventricle opaque. Pulmonary valve, sinuses indicated by three arrows on right.

FIG. 18. Case 7. (6 seconds) Pulmonary fibrosis and emphysema. Enlargement of pulmonary artery and conus. Right branch bracketed by arrows.

We have presented three main types of abnormality of the superior vena cava. The patient with Hodgkin's disease (figure 3) exhibited narrowing and displacement, the identity being established by its termination in the right auricle. The deformity of the superior vena cava in mediastinal and hilar tuberculosis (figure 12) suggests that such abnormality may reveal the presence of masses not otherwise demonstrable and therefore of value in the recognition of primary or metastatic neoplasm. Dislocation of the superior vena cava has been shown in figures 5 and 7. In case 3, in which excision of the tumor is planned, knowledge of the course of this vessel and the location of the heart will be of value. In the patient with fibrothorax (case 4), the position of the vena cava and heart is of academic interest.

Case 4 is of further interest since the chambers of the heart, the right pulmonary artery and veins and the aorta (figures 6 to 10) have been identified. The left pulmonary vessels could not be visualized.

Impairment or absence of opacification of the pulmonary blood vessels is shown in figures 8, 13, 15, 16 and 17. In case 5 interference with the circulation to the right lung by the hilar mass is probably responsible for this, especially since the pulmonary artery has been pushed to the left (figure 13). In the patient with bronchiectasis and fibrosis of the left lower lobe (case 6), the oblique views made possible recognition of the rotation of the heart, the origin of the pulmonary artery and its branches, and the absence of the large arterial trunk and numerous branches to the left lower lobe.

Case 7 (figure 18) illustrates another application of our method. It is now possible to identify the location of the chambers of the heart and to determine the site of hypertrophy. Parkinson and Hoyle (7), in their study of the heart in emphysema, call attention to the importance of recognizing enlargement of the pulmonary conus and the pulmonary artery at the hilum, and deplore their inability to measure enlargement of the individual chambers of the heart and the great blood vessels. Opacification of these structures now makes such information available.

Visualization of the pulmonary blood vessels in all positions enables one to form a more complete picture of structure and function and therefore offers a more satisfactory approach to the study of the pulmonary circulation. The vascular components of the mediastinum and hilum may now be seen and differentiated from nearby structures. Together with visualization of the chambers of the heart, this completes the contrast roentgenography of the thorax.

CONCLUSIONS

Mediastinal and hilar angiography is now a practical procedure. Its clinical application in pulmonary disease has been illustrated by case reports.

The information obtained by this technique is of diagnostic significance and offers a new approach to the study of the dynamic anatomy and physiology of the pulmonary blood vessels, the heart, and the great blood vessels in normal and diseased subjects.

We wish to express our thanks to Dr. J. Burns Amberson, Jr. for his encouragement in this study.

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BILATERAL ARTIFICIAL PNEUMOTHORAX[1]

BRUCE H. DOUGLAS, D. H. SALEY AND C. J. STRINGER

In a previous publication (1) it was shown that in our experience extensive collapse for the treatment of pulmonary tuberculosis probably has fewer contraindications and a wider range of usefulness than is at present appreciated.

Pursuant to this opinion, it was thought that support might be obtained and additional facts learned through a study of the experience of the staffs of Herman Kiefer Hospital and Maybury Sanatorium with simultaneous bilateral artificial pneumothorax during the last seven years.

It is essential to the present discussion to state that no attempt is being made to emphasize the merits of any one procedure over another in obtaining rest of the involved lung. With regard to bilateral pneumothorax, O'Brien (2) has stated, "If extensive disease with cavitation exists on both sides it is better to begin bilateral artificial pneumothorax early, without the use of phrenic operations, to minimize as much as possible the danger of spontaneous pneumothorax, which is much more serious if it occurs in the contra-lateral lung after the other lung has been greatly collapsed."

The purpose of the present study is to present a critical analysis of a group of patients treated by means of bilateral pneumothorax and observed over a period of one and one-half to seven years.

Since 1925 there have been many reports in the American and foreign literature concerning the use of bilateral artificial pneumothorax. Favorable experiences have been reported by Kinsella and Mattill (3), Corsello and Brackheimer (4), and Pollock (5) who have pointed out that bilateral collapse therapy has greatly increased the case group to which definite treatment may be applied. Couland (6) and Carmen (7) give contraindications which would deny active treatment to many of the patients in our present series.

This study has been made upon a group of 205 patients, all but two of

[1] From the Herman Kiefer Hospital, Detroit, and the Wm. H. Maybury Sanatorium, Northville, Michigan.

whom had far advanced bilateral disease at the time of admission and the majority of whom had definite bilateral excavations. Consideration has been given to the results obtained in those patients whose treatment was started between July, 1930 and April, 1936. Follow-up observations have been made up to January 1, 1938. Patients on whom treatment has been started since the above date are not included since it was thought inadvisable to attempt to estimate the results in any patient receiving treatment for less than eighteen months.

In the selection of cases for bilateral collapse only three groups of patients have been considered unsuitable: namely, those patients whose disease has resulted in marked toxicity and emaciation or dyspnoea; those with diseases impairing the respiratory function as silicosis; and those with diseases impairing the cardiorenal function. The patients in these three groups have already experienced a considerable reduction in the respiratory reserve and are unable to tolerate the further reduction made necessary by bilateral pneumothorax. Extensive bilateral lesions are, however, not necessarily a contraindication, if the general condition of the patient is such that he will tolerate collapse. The presence of tuberculous enteritis or osteomyelitis or laryngitis are not *per se* contraindications. Likewise it will be shown that other disease entities, notably diabetes, in the tuberculosis patient are not contraindications but are rather additional reason for the institution of adequate collapse measures. The work of Birkelo and Brosius (8) tends to show that in certain instances the pulmonary circulation is diminished due to fibrosis and thus the vital capacity is likely to be a false index of the cardiorespiratory reserve. The recent work of Jacobaeus (9) with the double bronchoscope and spirometer indicates that the lung is not always as efficient an oxygenating unit as the vital capacity might indicate. However, in the light of our present knowledge and resources for examination the most reliable single index to the tolerance of a patient for extensive collapse is still that patient's vital capacity. It is surprising to what extent the lung volume can be reduced and the patient be kept comfortable at bed-rest. In this series the vital capacity has been considerably reduced in all instances and markedly reduced (approaching the tidal air) in some of the patients. With hospital management this has not resulted in sufficient diminution of the cardiorespiratory reserve to cause embarrassment. Pleural adhesions are not always a contraindication. In this series there have been several such patients who have tolerated a positive intrapleural pressure on both sides. A patient on bed-rest can

certainly tolerate a vital capacity lower than that indicated by Carmen (2,000 cc.).

Additional surgical procedures were added as the need arose. There were 74 phrenic nerve operations on 65 patients, 16 pneumonolyses on 13 patients, and 11 thoracoplasties. In instances where thoracoplasty was employed, the pneumothorax on one side at least was not effective but the treatment had sufficiently improved the patients so that they could tolerate thoracoplasty. This group constitutes by far the most seriously ill of all the patients admitted to the hospital during the seven-year period for whom active treatment could be considered.

TABLE 1

CLASSIFICATION	PERIOD OF TREATMENT							TOTALS
	1 year or less	1–2 years	2–3 years	3–4 years	4–5 years	5–6 years	6–7 years	
Arrested	0	0	0	2	6	12	15	35
Apparently arrested	0	0	4	4	3	3	5	19
Quiescent	0	9	2	4	7	3	2	27
Improved	0	26	5	3	2	2	1	39
Unimproved	0	6	1	1	1	4	0	13
Dead	29	11	6	3	2	2	0	53
Unable to locate	0	1	2	2	2	7	5	19
Totals	29	53	20	19	23	33	28	205
Sputum negative*	0	25	9	13	17	20	22	106
Sputum positive	0	16	3	1	2	4	1	27

* Minimum requirements for calling a patient's sputum negative are a persistently negative sputum for at least six months to routine and concentrated examinations.

As those patients who have far advanced tuberculosis on admission are the most difficult to treat and the mortality rate is high any improvement in the way of lowered mortality speaks well for the procedure. At the Herman Kiefer Hospital the mortality among all those admitted as far advanced cases runs high.

In 1935, out of 710 cases, 257, or 36.2 per cent, died; in 1936, 273 out of 736, or 37.1 per cent; and in 1937, 246 out of 727, or 33.8 per cent.

When compared with the experience with the 205 cases treated with bilateral pneumothorax we find 29 deaths out of 205, or 14.1 per cent, in the first year and 53 out of 205 for the whole period of observation up to seven years, or only 25.6 per cent, which is a marked reduction in mortality.

In classifying the present status of these patients the standard of the National Tuberculosis Association has not been strictly adhered to, in that it is not thought advisable to classify as apparently cured any patient whose original disease has been extensive. Likewise, no patient who is still receiving pneumothorax, but is symptom free, has been given a better classification than quiescent.

Of the 205 patients studied, 120 are here classified as improved or better (table 1), 35 of these are arrested, 19 apparently arrested, 27 quiescent, and 39 improved.

As follow-up studies progress we hope to further reduce the number of patients whose present condition is classified as undetermined because of inability to locate them.

Of the 4 unimproved patients in the five to six-year group (table 1), two have recently allowed their lungs to reëxpand against advice during the course of a pregnancy and on reëxamination fresh infiltrations have appeared. There have been four other pregnancies in three of the arrested and apparently arrested patients all of whom have done well.

Only in the case of death, where of course the end result is known, have we included patients who have been under observation for less than one year. Note that more than half the deaths in the series occurred during the first year.

The percentage of deaths each year is illustrated in chart 1.

The immediate causes of death of 53 patients are as follows:

Increase of disease under collapse	11
Increase of disease following refusal to continue treatment	8
Haemorrhage	4
Increase of disease following reëxpansion in cases unable to tolerate collapse	3
Empyema and amyloid disease	4
Uncontrolled spontaneous pneumothorax	3
Cardiorenal disease	3
Enteritis	1
Atelectasis following second stage thoracoplasty	1
Circumstances unknown	15
	53 (25.7%)

The death from atelectasis following second stage thoracoplasty occurred at a time when we were not using bronchoscopy as extensively in tuberculosis patients. Otherwise the outcome in this case might have been different.

The death rate was higher in patients with tuberculous laryngitis and enteritis than in the entire group but of course these patients were more

seriously ill. There were 22 patients with enteritis and ten deaths in this group constituting a mortality of 45.4 per cent. The enteritis was directly responsible for death in only one case. Two of these 10 patients also had cardiorenal disease and 3 had syphilis. There were 10 patients

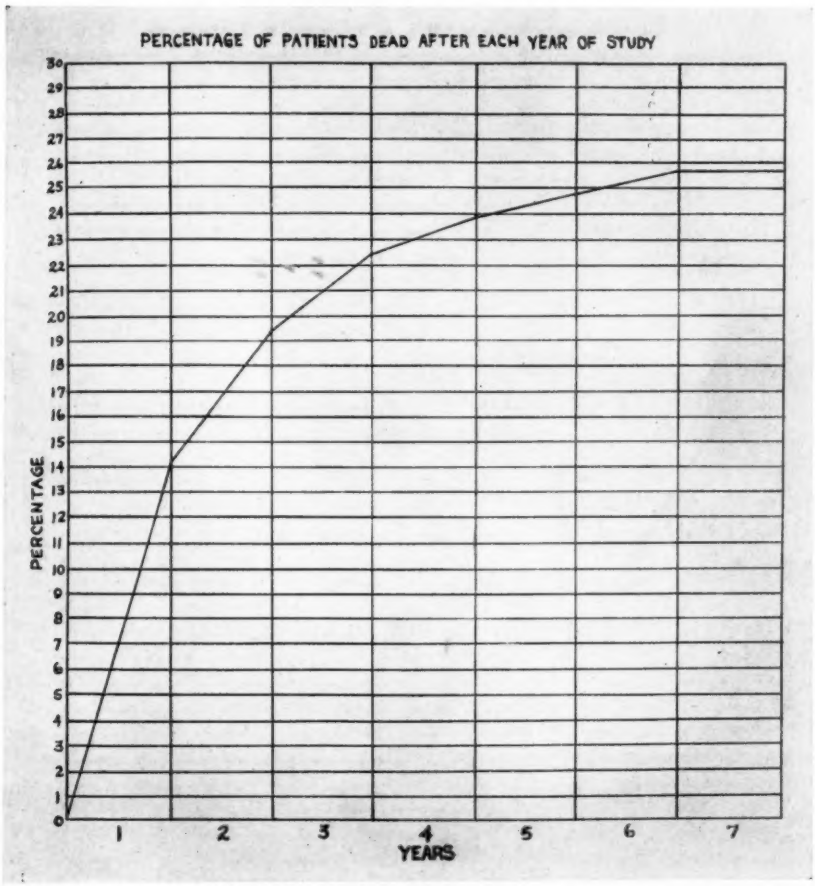


CHART 1. Representing the accumulative percentage of patients dead at the end of each year in the whole group of 205 patients.

with a complicating laryngitis and 4 of these patients are dead representing a mortality of 40 per cent in this group. The laryngitis was not directly responsible for death in any of the patients.

Of the 8 dead patients who refused treatment, two had a definite psychosis.

The one patient with renal tuberculosis is dead and 2 of the 3 patients with nontuberculous cardiorenal disease are dead. Two of the 3 patients with a known occupational fibrosis are also dead. The 4 patients in whom diabetes was present have all done well as long as they have had dietetic and insulin management. An adequate and balanced diet is given which is covered with the required amount of insulin. The other relatively infrequent complications have apparently played no part in the course of the pulmonary tuberculosis.

None of the lungs represented in the first two columns of table 2 were reëxpanded because of a sufficient period of collapse. Some of these were due to involuntary loss of space, some to an ineffective collapse, a few because of inability to tolerate collapse and others because of failure of the patient to coöperate.

TABLE 2

Survey of reëxpanded lungs

STATUS OF LUNG ON REËXPANSION	PERIOD OF COLLAPSE				TOTALS
	1 year or less	1–3 years	3–5 years	5–7 years	
Lung clear or cavity closed and infiltrations well fibrosed....	5 (25%)	41 (74.5%)	22 (81.5%)	7 (100%)	75 (68.8%)
Cavity patent and/or infiltrations not materially affected.....	12 (60%)	13 (23.6%)	2 (7.4%)	0	27 (24.8%)
Unable to locate.....	3 (15%)	1 (1.9%)	3 (11.1%)	0	7 (6.4%)
Totals.....	20	55	27	7	109

Sixteen of the patients in the three to five-year group were reëxpanded voluntarily and the 7 in the five to seven-year group were reëxpanded voluntarily.

Since the primary interest is not why the lungs were reëxpanded at varying intervals but what actually happened after treatment was discontinued, no classification has been made segregating the patients according to reasons for reëxpansion.

Naturally the percentage of good results has increased in direct proportion to the length of the period of collapse and similarly the percentage of poor results has decreased (table 1). All of the patients whose pneumothorax was continued for five to seven years have done well so far.

Many of those with cavity still patent and infiltrations not materially affected were reëxpanded in favor of other forms of surgery.

Only eleven of the reëxpanded lungs with an apparently good result at the time of reëxpansion have become reactivated and all of these were collapsed for less than five years (table 3).

TABLE 3*

Present status of lungs with an apparently good result at the time of reëxpansion

	PERIOD OF COLLAPSE				TOTALS
	1 year or less	1–3 years	3–5 years	5–7 years	
Roentgenogram unchanged	3 (60%)	26 (63.4%)	17 (77.3%)	6 (85.7%)	52 (69.3%)
Disease reactivated	1 (20%)	7 (17.1%)	3 (13.6%)	0	11 (14.6%)
Unable to locate	1 (20%)	8 (19.5%)	2 (9.1%)	1 (14.3%)	12 (16.1%)
Totals	5	41	22	7	75

* The patients represented in this table are the same as those in the first line of table 2.

TABLE 4*

Patients who have remained well following reëxpansion

PERIOD OF OBSERVATION SINCE REËXPANSION	PERIOD OF COLLAPSE				TOTALS
	1 year or less	1–3 years	3–5 years	5–7 years	
1 year or less	0	2	1	2	5
1–2 years	1	1	2	3	7
2–3 years	0	5	2	1	8
3–4 years	2	4	4	0	10
4–5 years	0	10	8	0	18
5–6 years	0	4	0	0	4
Totals	3	26	17	6	52

* The patients represented in this table are the same as those in the first line of table 3.

Of the 3 who became reactivated in the three to five-year group, two are the patients who against advice allowed their lungs to reëxpand during the course of pregnancy.

As the study progresses the unchanged group is increasing at the expense of the undetermined group. Table 4 indicates the varying periods of observation following reëxpansion in relation to the duration of the collapse.

Complications have not been greatly different from those encountered in unilateral artificial pneumothorax. There were 42 instances of uncomplicated and transitory pleural effusion. There were 16 cases of empyema, 9 instances of spontaneous collapse and 4 of the patients became too dyspnoeic to continue treatment. There was a rather marked kinking of a bronchus in one patient in whom the pneumothorax had to be abandoned.

Brief Representative Case Reports

Case 1: D. B., no. 9291, age 15 years, admitted to the hospital July 12, 1930, with a negative sputum but with X-ray evidence of far advanced exudative disease with bilateral cavities (figure 1). Left artificial pneumothorax was started in July, 1930, and right artificial pneumothorax was started in September, 1930 (figure 2). She developed a pleural effusion in December, 1932, which resulted in loss of the left pleural space, following which she had a left phrenic nerve crushing. The right pneumothorax was discontinued in February, 1937. She is sputum free and doing her own housework. She had a normal delivery in May, 1936, and another in August, 1937, and the lesions in both lungs have remained apparently healed (figure 3).

Case 2: C. S., no. 11969, age 23 years, diagnosed as far advanced pulmonary tuberculosis with bilateral excavations in October, 1931 (figure 4). Hospitalization was delayed because of the wishes of the patient, but pneumothorax was started on the left side on January 2, 1932, and on the right side on January 20, 1932 (figure 5). The bilateral pneumothorax was continued until July, 1934, when the right side was discontinued following a pleural effusion. He was discharged to the out-patient department in October, 1935. The left pneumothorax was discontinued in December, 1936. He is in excellent condition and is working. The film made in September, 1937 (figure 6) shows well healed lesions in both lungs.

Case 3: H. Z., no. 8852, age 16 years, admitted to the hospital in March, 1930 (figure 7). She was classified as III-B favorable, with an associated diabetes mellitus. Bed-rest was the only treatment given at that time due largely to the attitude of the patient and her family. She left the hospital against advice in July, 1932, and we did not hear from her again until January, 1935, at which time she was examined in the out-patient department and the tuberculosis had apparently become arrested. Following this examination she refused adequate management for her diabetes, and when seen again in November, 1935 (figure 8) she had a marked increase of disease in both lungs with a positive sputum. She was quite ill. The blood sugar was 400 mg. and the

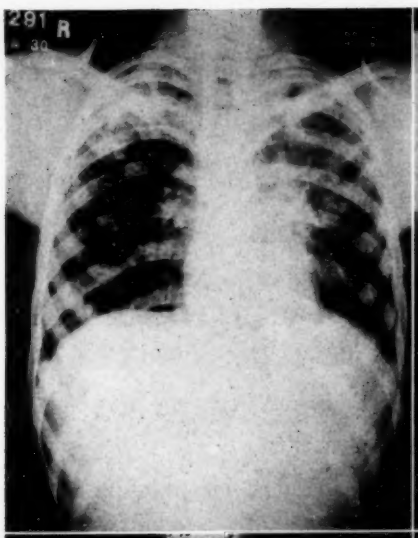
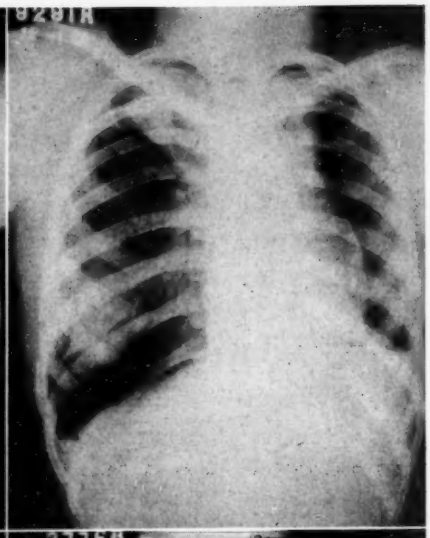


FIG. 1



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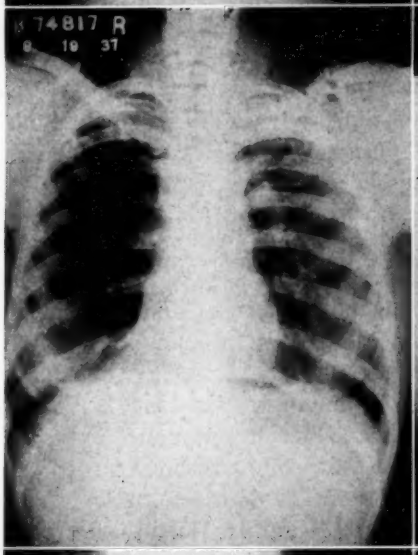

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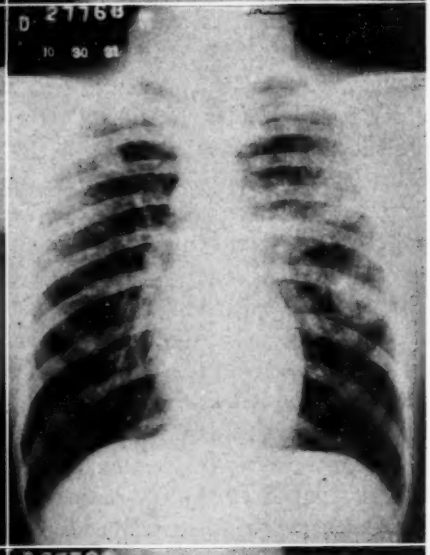

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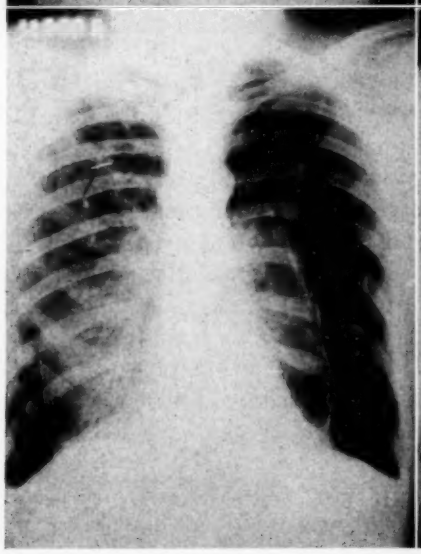

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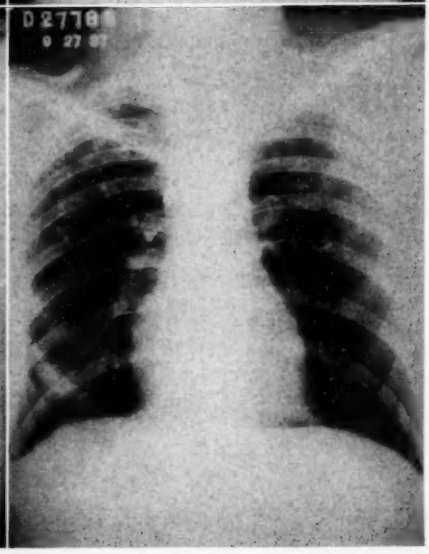

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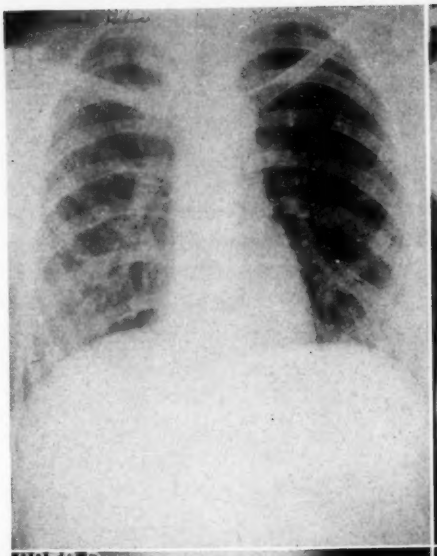

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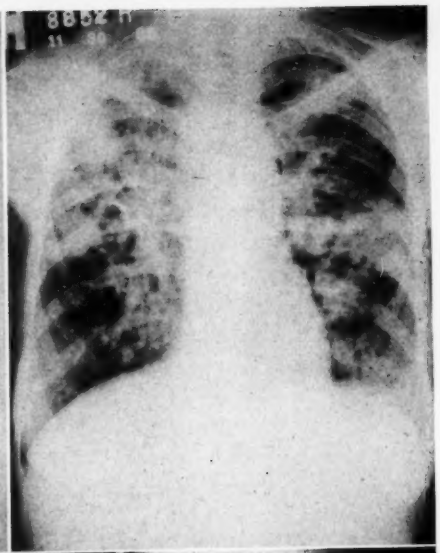

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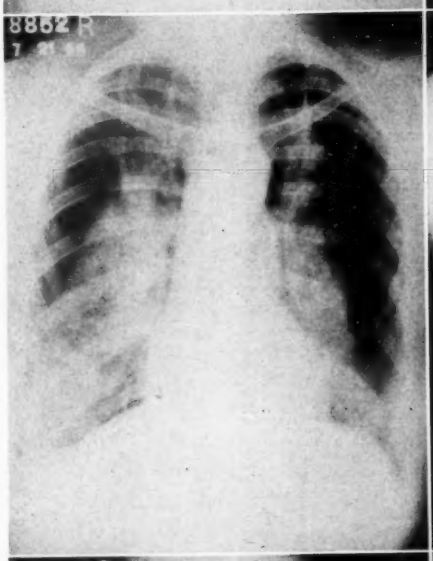

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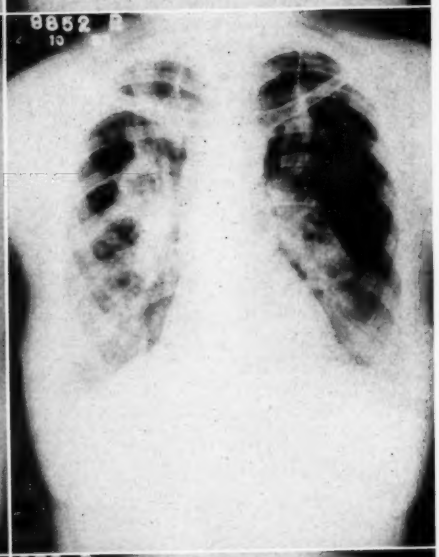

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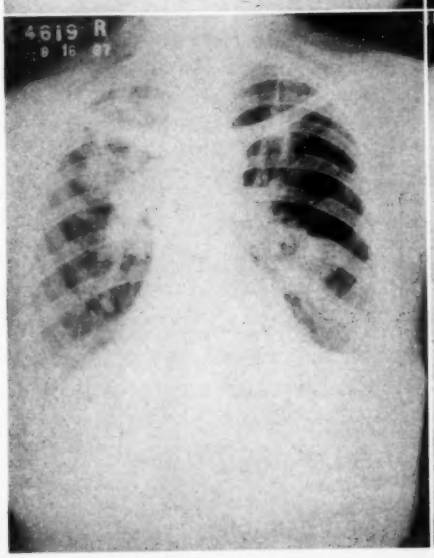
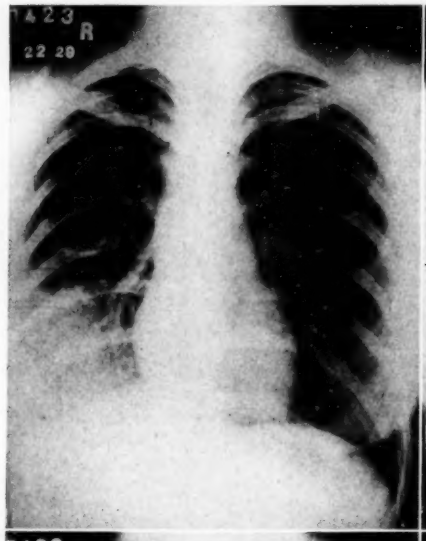


FIG. 11

FIG. 12

leucocyte count 24,000. At the time of readmission two months of observation and an attempt to control the diabetes was the treatment of choice. She improved somewhat and right artificial pneumothorax was started in Febru-



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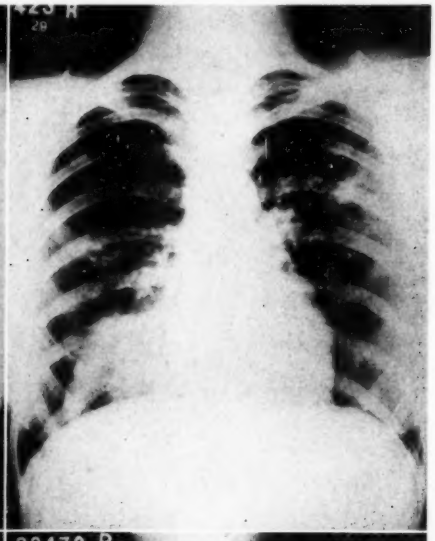

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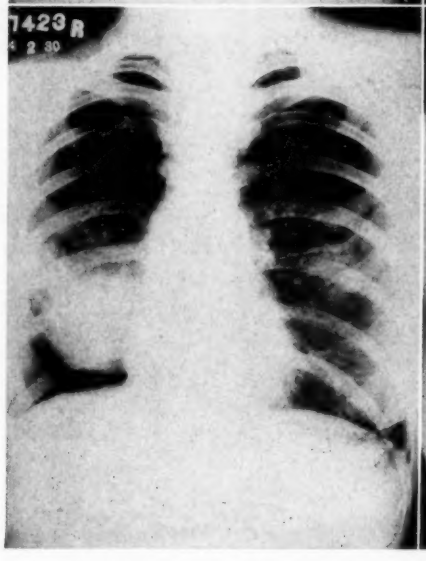

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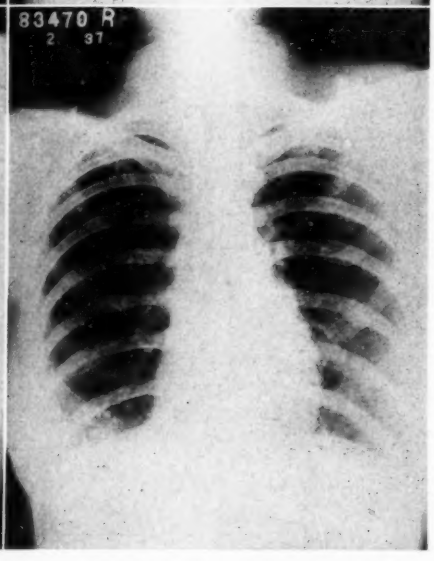

FIG. 16

ary, 1936, and left artificial pneumothorax in March, 1936 (figure 9). She was sputum negative and essentially symptom free following the institution of the bilateral artificial pneumothorax and was discharged to the out-patient de-

partment in April, 1937 (figure 10). She again disregarded dietary instructions and insulin therapy, and failed to come to the clinic regularly. The film taken in the out-patient department in September, 1937 (figure 11) showed a complete loss of the pneumothorax space on the right side with reappearance of the excavations and partial reëxpansion of the left lung. She has again been hospitalized and the diabetes is now fairly well controlled. Pneumothorax could not be reëstablished on the right and therefore she was given a right phrenic nerve crushing. Considerable improvement has again resulted during the brief period of her more recent hospitalization (figure 12). This case exemplifies the relapse of an apparently arrested tuberculosis concurrent with gross neglect of an associated diabetes and a second relapse after treatment was again refused. In the four diabetics in the group, the diabetes has been more adequately and more easily controlled with the institution of collapse, and similarly the tuberculosis has been aided by adequate management of the diabetes.

Case 4: M. L., no. 7423, age 18 years, admitted January 21, 1929, with advanced pulmonary tuberculosis with a 3 cm. cavity in the base of the right lung. The left lung was clear (figure 13). Right artificial pneumothorax was started on January 28, 1929. The film made July 12, 1929 showed fresh infiltrations in the left lung with a 3 cm. cavity (figure 14). Left artificial pneumothorax was therefore started on July 18, 1929, and a satisfactory pneumothorax space obtained (figure 15). The right lung was voluntarily reexpanded in January, 1935. The left lung was voluntarily reëxpanded in March, 1936. She was discharged to the out-patient department in May, 1936, and has been doing all of her own housework since August, 1936. She has continued symptom-free and sputum-negative, and X-ray examination shows very little evidence of the former disease (figure 16).

DISCUSSION

Fortunately for patients with pulmonary disease, there exists a large functional reserve in the lung which may be called into play by increasing demands upon the respiration. This intrinsic lung function possesses a power of prompt adaptation to the changing demands made upon it. It is because of this large cardiorespiratory reserve that our present methods of therapeusis in pulmonary tuberculosis are rational and successful. It is the object of the phthisiotherapist to establish a balance between a patient's need for collapse therapy and his tolerance for the indicated procedures. This tolerance on the part of the patient has permitted surgery to assume its present rôle in the therapy of phthisis.

It is still common practice in some clinics to allow in the majority of cases a period of observation of three to six months on bed-rest alone. Such an attitude denies the patient the additional aid of collapse therapy for the period of time during which the disease is likely to be most destructive. Douglas, Nalbant and Pinner (10) in their study of *Acute Subapical versus Insidious Apical Tuberculosis* point out that lesions may become far advanced within less than six months. Obviously three things may happen to a patient following a period of bed-rest alone, that is, he may become worse, he may remain practically stationary, or he may improve. In the first instance valuable time has been lost and the problem of effective therapeusis has become greater. In the few cases who remain essentially unchanged the period of observation might be justified, but who is there to predict which case of active tuberculosis will remain unchanged? It is probable that the majority of patients who are placed on bed-rest alone will improve temporarily but this very fact becomes a danger in that it leads to a false sense of security. Much time is saved and much risk is avoided by promptly augmenting bed-rest with collapse therapy.

Barnes and Barnes (11) in their exhaustive study of the fate of patients with cavernous phthisis reported a 100 per cent mortality at the end of seven years in patients with bilateral apical cavities diagnosed by X-ray, and an average duration of life of seven months. They further reported a mortality of 96 per cent in all bilateral cavity cases regardless of the location of the cavities. Of 89 cases with tuberculous laryngitis 79 died within a year, and of 17 cases with tuberculous enteritis none survived a year.

Schwatt and Rest (12) without mentioning the type of treatment given reported a mortality of 62 per cent in 267 patients after periods of observation of from three to ten years. These patients had cavities in one or both lungs. Only 17 per cent of their patients with tuberculous laryngitis were still alive and only 1 per cent of those with tuberculous enteritis were still alive.

It would appear from our experience with this group of patients that when extensive bilateral disease exists, particularly in the presence of bilateral excavation, it is best to start artificial pneumothorax on both sides at once. The program of treatment is not adequate if an attempt is made to cause the improvement or arrest of the disease in one lung before starting treatment on the other side. If effective bilateral arti-

ficial pneumothorax is not possible then it is advisable to proceed with some other combination of collapse procedures.

Pregnancy has been well tolerated in patents classified as arrested or apparently arrested. The patients who have allowed their lungs to re-expand during the course of a pregnancy have relapsed. For this reason it seems advisable to impress these people with the necessity of continuing partial collapse during the course of a pregnancy and for several months at least thereafter.

Emphasis is again given to the often repeated observation that the percentage of good results is in direct proportion to the duration of the collapse. The number of subsequent reactivations progressively decreases with the length of the period of collapse. Pneumothorax should be maintained for at least five years in patients with extensive cavernous disease. A longer period of collapse is usually advisable.

SUMMARY

A group of 205 patients seriously ill with far advanced bilateral pulmonary tuberculosis has been observed for periods of from eighteen months to seven years. Each of these patients has been treated with simultaneous bilateral artificial pneumothorax.

These patients as a group represent the most seriously ill of all the patients who have had active treatment during this period of time.

A classification of improved, quiescent, apparently arrested or arrested has been given to 120, or 58.5 per cent, of these patients; 13 patients, or 6.2 per cent, are unimproved; 53, or 25.7 per cent, are dead and the status of 19, or 9.2 per cent, is as yet unknown.

The effectiveness of the treatment is uniformly in direct proportion to the length of the period of collapse and thus far there have been no relapses in those patients whose lungs have been reëxpanded after seven years of pneumothorax.

Pregnancy was not tolerated well during the process of allowing the lungs to reëxpand but patients in the apparently arrested and arrested groups who have become pregnant have done well.

More than one-half of the deaths have occurred during the first year of treatment, but after the first year those who are under a satisfactory collapse do exceedingly well and there are relatively few deaths.

One hundred and nine lungs have been reëxpanded because of sufficient period of collapse, or ineffective collapse, or inability to tolerate

collapse, or refusal of the patient to continue treatment, and of these 109 lungs, 75 were apparently healed at the time of reëxpansion, and of these 75 lungs, 52 are known to have remained apparently healed. The disease has become reactivated in 11 and the present status is unknown in 12.

Contraindications are limited almost entirely to patients with marked emaciation and toxicity or with diseases impairing the respiratory function, such as occupational fibrosis, or with diseases impairing the cardiorenal function, that is, those patients who already have experienced a considerable reduction in their cardiorespiratory reserve. Tuberculous lesions in other organs and other disease entities in the tuberculous patient are not *per se* contraindications.

The frequency of complications and the character of complications have not been greatly different from those observed in the same number of collapsed lungs in unilateral artificial pneumothorax.

CONCLUSIONS

1. Bilateral simultaneous pneumothorax in patients with far advanced bilateral pulmonary tuberculosis is a feasable procedure and of considerable benefit in the majority of instances.

2. Contraindications are limited to those conditions which produce a diminution in the cardiorespiratory reserve.

3. Of the patients thus treated during the last seven years, 58.5 per cent are known to be doing well and 25.7 per cent are known to be dead.

4. There is sufficient evidence therefore to warrant the opinion that the prompt institution of bilateral simultaneous artificial pneumothorax should be the treatment of choice for those cases of pulmonary tuberculosis where extensive disease with cavitation exists in both lungs.

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END RESULTS OF THORACOPLASTY[1]

LE ROY S. PETERS AND P. G. CORNISH

Thoracoplasty has now become a recognized procedure in the treatment of suitable cases of pulmonary tuberculosis. Even those who hesitate where angels fear to tread and who still believe that tuberculin is a specific for pulmonary disease, occasionally advocate chest surgery after years of vainly attempting to stretch unburnable adhesions in an incomplete pneumothorax.

On the other side of the fence we find the over-enthusiastic tuberculosis specialist in collaboration with his chest surgeon imbued with the idea that, by depriving the patient of sufficient lengths of rib, the tubercle bacillus will be deterred from pursuing its deadly course. Euthanasia is indicated in both groups.

The literature on collapse therapy is filled with results and these statistics vary with the enthusiasm of the author. They also vary with the caution of the chest surgeon and his medical ally. There are many men who have a feeling for perfect results, and where a certain risk appears will condemn that patient to a consumptive's grave rather than take the chance of adding a death to their otherwise perfect record. These are the operators who report a high percentage of excellent results, cavity closure, sputum eliminated or, if present, negative for the tubercle bacillus and 80 per cent of patients back in the harness, leading normal lives and probably helping to swell the ranks of the unemployed.

There is the third class of physicians who are forced to choose patients from the ranks of other men's failures or from patients who have become failures through their inability to take good advice. This class of patients represents the old chronic with thick-walled cavity and surrounding dense fibrosis who has become a poor surgical risk from long years of tuberculosis, but who must be given his one chance of a restoration to his place in society. We see this type of patents in all sections of the country but we see them especially in the desert regions of the Southwest. They have tried all types of physicians, all types of en-

[1] Presented at a session of the 33rd annual meeting of the American Sanatorium Association, Los Angeles, California, June 20, 1938.

vironment, home and sanatorium, with no success. As a last resort they change climates, and we who dedicate our lives to suffering humanity are the victims of this last chance. We pick the majority of our surgical risks from this type of patient, and our results are therefore not comparable to those of our more fortunate colleagues in a more favorable environment, and unquestionably not comparable to those of the surgeon or internist who wants a written guarantee that the patient is a 100 per cent operative risk before even suggesting the possibility of chest surgery. We do not consider that we are in competition with this type of medical mind. We are in the practice of medicine to do what we can to restore the pulmonary invalid to a place in the economic scheme and, with that attitude toward life, give to what sometimes appears a hopeless risk a chance for a life of usefulness.

Do not gather from this statement that we advocate surgery for all and every type afflicted with pulmonary tuberculosis. We still choose patients with an idea to end results, and the tabulation of such results will convince the man of average tolerance that we are justified in this attitude. We feel that, based on general averages over the country, our percentage over the years compares very favorably.

The actual technique of the operation has been so standardized that it does not seem to us that failure of cavity closure can be blamed on the surgeon. Successful closure is sure in 90 per cent of early types with grape skin cavities, but the same percentage cannot be claimed for thick-walled cavities in dense fibrous lung. Here, even with the removal of the upper three ribs in their entirety, the lung fails to drop to any great degree and many times, even after the succeeding stages, the cavity will still be found, though reduced in size. Failure comes in these very ill patients often because too much time must elapse between stages to let a heart muscle recuperate from the strain of the initial operation. Occasionally an infected wound must be cleaned up, which delays the second stage. With this delay regeneration of bone takes place, all of which must be removed at subsequent operations. This in itself adds to the operative risk which is sometimes more than a weak heart muscle can withstand. Operative deaths result from cardiac failure in the majority of cases. Atelectasis if massive may cause death from anoxaemia. Embolism is rare as in other types of surgery. The mortality after operations are completed follows extention of the tuberculous process in the contralateral lung, or where cavity closure has been unsuccessful a

gradually progressing tuberculosis. Hearts and kidneys may close the picture many months after apparently successful surgery.

As the years have passed, experience has taught us a "lot, that has helped us a lot, of the things that we ought to know" and to-day the mortality has been greatly reduced so that we can advise a thoracoplasty as calmly as one would advise the more serious types of abdominal surgery.

We have elected to report the end results in a small series comparing the old with the new type operation. To show how small a number can be traced in private practice we are able to report on but 78 cases in a series of over 300.

There were 40 patients on whom a complete thoracoplasty was performed, that is, removal of sections of first through the eleventh rib; 21 per cent of this number were made well (negative sputum and cavity closed), while 54 per cent are dead. All these patients were hopelessly ill and would ultimately have died had it not been for surgery. None was able to work even part time. The others are living with positive sputum and open cavity, no better than before operation and will ultimately die of tuberculosis.

The deaths in the 40 patients occurred as follows: 22 of cardiac failure within four weeks after operation; 1 intestinal tuberculosis eight weeks after operation; 3, one appendectomy one year after operation and two empyema one year after operation; 2, one empyema five years after operation and one contralateral extension five years after operation.

There were 38 patients on whom a partial thoracoplasty was done, that is, complete removal of the first three ribs plus sections of others sufficient to cover the lesion; 50 per cent of this number were made well (cavity closed, sputum negative) and 34 per cent are dead. The others, like the old operation cases, still show positive sputum, open cavity and are unable to work. They, too, will no doubt die of tuberculosis. The same can be said of this group as of the other—had surgery not been done all would have died of their disease.

The deaths in the 38 patients occurred as follows: 13, twelve cardiac failure one week or longer after operation, and one acute dilatation of the stomach one week after operation.

In the early years few patients with disease in the contralateral lung were considered safe risks for chest surgery. In our series of 40 cases the opposite lung was supposed to be normal, while in our series of 38, twelve had disease in the contralateral lung. With the newer type oper-

ation, however, a much greater chance can be taken with contralateral disease. In fact the indications for thoracoplasty are about the same as for pneumothorax.

It is also interesting to note that under the old operation only 21 per cent were made well and 54 per cent died, while under the new 50 per cent were made well and 34 per cent died. Thus does experience and new technique make better doctors of us all.

These end results, as well as others reported in the literature, should be convincing proof that all patients who must otherwise die of their tuberculosis should be given the benefit of surgery if they offer a fighting chance for recovery. To do less is to sacrifice lives that might otherwise be saved. All those reported well have been so from two to fifteen years. We have patients living and working to-day in excellent health whose thoracoplasties were done fifteen years ago. Working for a clean record sheet, attempting to avoid operative deaths through fear of risk, dooms many consumptives whose lives might be turned into useful channels. After all is said and done, is not the physician's usefulness to society measured by the lives he saves?

EVENTRATION OF THE DIAPHRAGM

Report of a Case

J. W. STRAYER

Eventration of the diaphragm has long been a source of confusion in the differential diagnosis of diseases of the chest and abdomen. One reason for this is that the symptoms are usually referable to the abdomen, while the physical signs are found in the chest. The term as generally used means an unnaturally high diaphragm. This is often confused with hernia, in which the diaphragm is at its normal level except for that part which forms the sac, the abdominal contents escaping through a relatively small foramen. The anomaly was first recognized by Petit (1) in 1774. Reed and Borden (2) in a critical review of the literature reported a total of 183 collected cases. It is significant that 165 of these cases were on the left side.

Aetiology: Although various causes are cited for the anomaly, such as trauma, tuberculosis, peptic ulcer, gastric carcinoma, neuritis and degenerative changes of the phrenic nerve, muscular atrophy and fibrosis of the diaphragm, there is a preponderance of evidence that it is congenital in origin (3 and 4).

Symptoms: The patient usually complains of indigestion, cramping pains in the abdomen and perhaps vomiting, depending somewhat on which organs are displaced. In the author's case, although the abdominal symptoms predominated, the patient had had a chronic cough for years. Dyspnoea was also very pronounced.

Case Report

This patient, a white male of age 56, was first examined at a chest clinic in December, 1937. One week prior to this the patient had expectorated a small amount of blood which he thought came from his lungs. Two months prior the patient had felt very tired and had lost seven pounds in weight. The family and past history were irrelevant except for alcoholism and a chronic dry cough of many years' duration. His general health had been fair except for two attacks of severe abdominal pain accompanied by nausea and vomiting. The first of these attacks was thirty years ago at which time he was operated on for "appendicitis," but was told after the operation that the appendix was not found. Recovery was uneventful. Although he was bothered intermittently with indigestion, flatulence and cramp-like pains in the abdomen

there had been no severe attacks until ten years ago. The patient was examined by roentgenogram and was told that his viscera were either reversed or peculiarly disposed. He was treated medically and had practically no intestinal symptoms thereafter.

Physical examination: The patient was fairly well nourished and well developed. His face was florid, his flesh was soft and flabby and he had the general appearance of an alcoholic. There was a marked tremor of the fingers. Except for the chest and abdomen the physical examination was noncontributory.

Heart: The apex was not palpable nor could the cardiac borders be accurately percussed. On auscultation the heart sounds were loudest in the fifth intercostal space in the right parasternal line. No murmurs were audible. Blood pressure was 150/80.

Chest: There was a relative fixation of the entire thoracic cage. There was retraction of the suprasternal notch on inspiration. Both costal margins retracted during inspiration (Hoover's sign). This was more marked on the left side. Right lung: Scattered crackling râles were audible. Left lung: Tactile fremitus was diminished below the third rib anteriorly and the eighth dorsal spine posteriorly. The percussion note was dull over these same areas except in the midaxillary line where it had a tympanitic quality. Posttussic crackling râles were audible just beneath the clavicle and over the spine of the scapula. Borborygmi were audible at the level of the third rib anteriorly, the eighth rib posteriorly and in the midaxillary line. Breath-sounds were absent over this area. The patient became quite dyspnoeic after coughing. Vital capacity was 800 cc.

Abdomen: A large deep McBurney's scar was visible. Normal to palpation.

X-ray of the chest: The bony cage was normal. The mediastinum was shifted to the right and the heart shadow was directly beneath the sternum. The right leaf of the diaphragm was smooth and rounded and of normal conformation. The left diaphragm was obscured by a dense shadow with a slightly curved margin following the course of the seventh intercostal space posteriorly. (It was later found that that which appeared to be a "fluid level" was in reality the diaphragm itself.) The right lung was normal except for a Ghon's tubercle lying just above the diaphragm. Left lung: The only lung tissue visible was above the third rib anteriorly. At this level the left chest was sharply demarcated by a horizontal line beneath which there was uniform and absolute opacity, except for a narrow vertical band of lesser density at the periphery. The markings were faint but they suggested an air-containing viscus which did not simulate lung tissue. The visible lung tissue in the apex was much less dense than the right lung (figure 1).

A barium meal was given and the stomach was found to be in the pelvis. Another film in twenty-four hours demonstrated the presence of the colon high up in the left chest. A barium enema the following day revealed that all

of the colon except the caecum was above the normal level of the diaphragm. Beginning at the ileocaecal valve which was approximately at the normal level of the diaphragm, the colon extended upward to the third rib anteriorly and then flexed sharply laterally and descended to the rectum.

On the first film immediately after the enema the inverted U-shaped segment of colon was so greatly distended with barium that it occupied the entire pleural space from the midline to the lateral wall. After expulsion of most of the barium the colon was greatly reduced in diameter and its course was more clearly discernible than in the first film (figure 2).

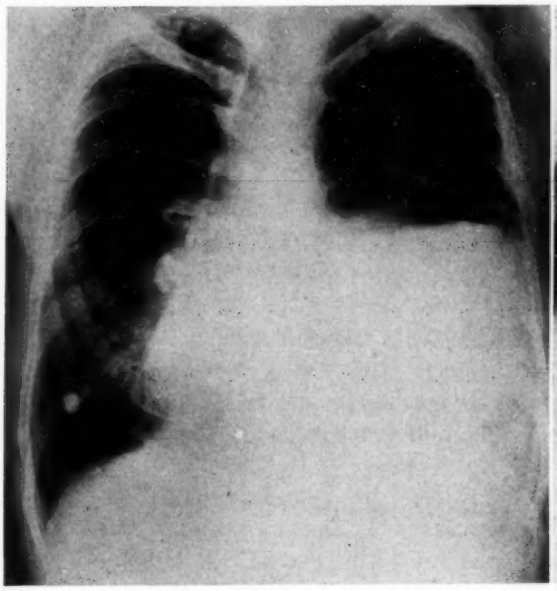

FIG. 1

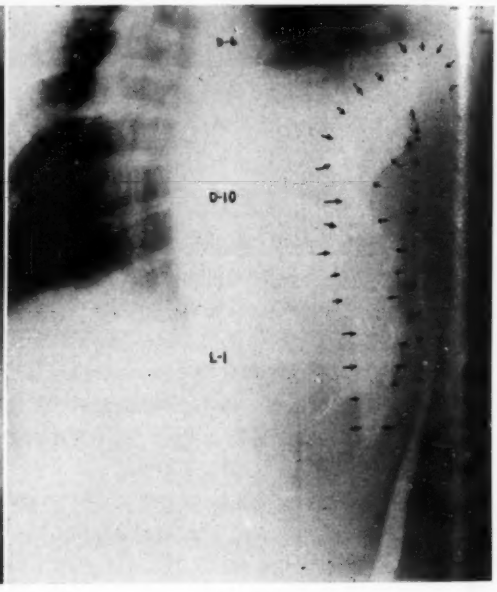

FIG. 2

FIG. 1. Eventration of left hemidiaphragm. Note displacement of mediastinum to right and rarified left lung.

FIG. 2. Film following barium enema. The caecum and what may be the appendix are visible in the left upper quadrant. The "ascending" colon has been slightly retouched.

Fluoroscopy: There was paradoxical movement of the diaphragm, the right leaf moving down in inspiration, the high left leaf moving upward.

COMMENT

The diagnosis of eventration of the diaphragm is practically impossible by means of physical signs. Korns (5) has placed great stress on the motion of the costal margins (Hoover's sign), arguing that with a high hemidiaphragm the unopposed action of the intercostal muscles would result in a wide flare on the affected side. In this case, however, there

was retraction of *both* costal margins which was much more marked on the involved side than the normal side. In no way therefore could the costal movements be interpreted as being due to eventration. It has been stated (2) that respiratory movements may be normal, diminished, absent or reversed in either eventration or hernia.

Even the X-ray diagnosis is not easy since the picture may be confused with pleurisy (with or without effusion), an encapsulated empyema, subdiaphragmatic abscess, carcinoma and other similar entities. The case cited above was first thought to be a pleural effusion and the patient was tapped after the first preliminary examination. Fortunately enough the bowel was not entered and the patient suffered no ill effects. The gurgling sounds due to the motion of fluid and gas in the colon were inconstant and audible only at times when the colon was full.

Moore and Kirklin (6) emphasize the importance of contrast media in the differential diagnosis of eventration or hernia. This leads one to the correct diagnosis, providing that the organ displaced is either stomach or intestine. As in this case it may be necessary to give the barium by rectum, depending upon which part of the intestinal tract is involved. When other organs such as the liver or spleen are involved, pneumothorax may be employed to good advantage in making a diagnosis.

Another complicating factor in this case was the large amount of pulmonary emphysema present. The small "thinned out" left lung may be noted in figure 1, but this alone would not account for the unusually small vital capacity of 800 cc. The physical signs, namely, the rigid chest, the absence of Litten's sign and the retraction of the costal margins and suprasternal notch, tend to support this diagnosis.

SUMMARY

A case of eventration of the diaphragm has been presented, the diagnosis of which was not clear until an X-ray film following a barium enema revealed the high position of the colon.

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PULMONARY EMPHYSEMA IN TUBERCULOSIS[1]

EPHRAIM KOROL[2]

DEFINITION AND CLASSIFICATION

Emphysema is an atrophy of the lung, characterized by anaemia and stretching of the alveoli, with rupture of the interalveolar septa. Functionally, the emphysematous lung has decreased elastic recoil and diminished power of expiration, with consequent accumulation of residual air. Roentgenographically, there is increased radiolucency and a diminution in the number of vascular shadows. Anaemia of the lung is a constant and most important factor. It may be caused by atherosclerotic changes involving the pulmonary (1, 2) or the bronchial (3, 4) arteries, and less commonly by endarteritis or thrombosis of these vessels. The overinflation of the lungs which occurs in bronchial asthma, in bronchial stenosis of whatever cause, and in dyspnoeic states is soon followed by emphysema, that is, by ischaemia of the lung with impaired elasticity. As no new blood vessels can form in the adult lung, the enlarged lung is necessarily poorly nourished. The lung at best is poorly supplied with nutrient blood. The bronchial artery is the smallest of the visceral arteries, and of all the organs, the lung is most subject to atrophy, gangrene, infarction, and other vascular insults. The pulmonary anaemia in emphysema may thus be primarily vascular in origin, or it may be secondary to stretching of the lung.

The lung is often stretched by atmospheric pressure to fill space newly created in the chest by collapse or fibrosis of certain portions of the lung. This compensatory or complemental emphysema also presents an atrophy rather than a hypertrophy of the lung (5) and it shows the same roentgenological (6) and histological findings of lung atrophy (7) as do the other forms of emphysema.

CAUSES OF EMPHYSEMA IN TUBERCULOSIS

The diffuse emphysema associated with pulmonary arteriosclerosis is not often seen in tuberculosis, due to the youth of the patients and the infrequent association of cardiovascular disease with tuberculosis. Lo-

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calized or bullous emphysema is more often seen and is attributable to thrombosis and obliterative endarteritis. The bronchial artery may be invaded by caseous lymph nodes in the mediastinum before the artery reaches the lung; more often the smaller arteries are involved by extension of the tuberculous process from within or without the bronchus. The main pulmonary artery is seldom the seat of tuberculous changes, but the smaller arteries often show specific and nonspecific inflammatory changes. These lesions in the bronchial and pulmonary vessels in tuberculosis were recently studied by Bezançon and Delarue (8), Menetrier (9), Ameuille (10), and Derscheid and Toussaint (11) described the various pathological changes in the bronchial arteries. The changes in the pulmonary vessels have been studied by many pathologists, more recently by Ameuille and his coworkers (12), and in this country by Pou and Charr (13).

But it is the compensatory form of emphysema which is most often seen in tuberculosis. It sometimes reaches spectacular proportions, and may lead to lung hernia and to spontaneous pneumothorax (figure 9).

The roentgen appearance in compensatory emphysema is the same as in other forms of emphysema; there is a decrease or absence of vascular shadows, there is increased air content, which diminishes but little in expiration, and there may be annular shadows of large emphysematous vesicles. Upon injection of opaque solutions into the pulmonary artery it has been shown that the blood vessels are decreased in size and number when compared with the healthy portions of the lung (Ameuille and Hinault (14)); the injected blood vessels are often the seat of endarteritis and thrombosis (Pou and Charr (13)).

CONTRIBUTORY FACTORS

Bronchial stenosis frequently occurs in tuberculosis and may depend on a variety of intrabronchial or extrabronchial lesions. Emphysema associated with bronchial stenosis in tuberculosis has been described by several authors (Spivek (15), Faust (16)). The attacks of coughing and the labored breathing are also predisposing factors.

The loss of weight with the consequent descent of the diaphragm and decrease in the size of the heart also tends to stretch the lungs in tuberculosis.

EMPHYSEMA IN THE SEVERAL FORMS OF TUBERCULOSIS

While acute emphysema has been described in miliary tuberculosis (17) and in caseous pneumonia (18), extensive emphysema is typically

seen in the more fibroid types of tuberculosis. In the exudative lesions the vascular injury is overwhelming, leading to complete tissue necrosis with caseation and liquefaction. At the periphery of the lesions the circulation, due to collateral anastomosis, is sufficient to prevent necrosis, but the musculo-elastic reticulum of the lung is often impaired in nutrition, and there is loss of elastic recoil. This has been referred to as emphysema of healing (19), emphysema of absorption (20), and emphysema of scar tissue (21). The apparent arrest of the tuberculous process by emphysematous lung led to the belief of the earlier pathologists that tuberculosis and emphysema are mutually antagonistic, and it was recommended that emphysema be produced artificially in the treatment of tuberculosis (22).

Pulmonary emphysema about the primary complex: Extensive emphysema may occur during the active stage of the primary complex and is generally caused by the encroachment of the enlarged lymph nodes either on the bronchial artery or on the lumen of the bronchus (16, 34); more often emphysema is seen about the healed parenchymal component.

Bullous emphysema in healed apical tuberculosis: This is one of the commonest types of emphysema. In our clientele of middle aged veterans it occurs in about 30 per cent. The condition gives no symptoms or physical signs, but produces a rather typical X-ray appearance. The apex is more transparent than usual; the normal vascular markings are absent; instead, there is one or more crescentic lines representing thickened interlobular septa. These lines are convex outward and downward. In several cases we have observed these bullae to enlarge and to coalesce in the course of years. Rupture of one of these vesicles is the usual cause of the spontaneous pneumothorax occurring in the absence of clinical tuberculosis. Huebschmann (17) shows beautiful illustrations of this type of emphysema. Several observers (Dorendorf (23) and Zinn (24)) have found that the tuberculous scars produced strictures in the bronchioli, which acted in a ball-valve manner. In some of Kjaergaard's (25) cases no such valvular mechanism existed. Bronchial stenosis is not essential for the production of emphysema. Loss of elasticity from whatever cause prevents proper expiratory deflation of the involved lobules and leads to progressive emphysema.

Bullous emphysema in progressive tuberculosis: In fibrocaseous tuberculosis of slow evolution, large emphysematous bullae are often recognizable on the roentgenograms. They increase in size and number with

the advance of the disease. They can be differentiated from tuberculous cavities by their thin walls, by the absence of infiltration in the immediate vicinity, and by the greater transparency due to the lack of overlying thickened pleura. They are usually situated in the apices and cause no symptoms, this part of the lung not being very active functionally.

When situated in the base of the lung, dyspnoea is usually marked and there is often wheezing respiration resembling asthma.

The most pronounced cases of emphysema that we have encountered were in cases of fibrocalcareous tuberculosis of many years' duration, with multiple calcifications in the lungs and hilum lymph nodes. In Sweany's cases (20) of multiple calcifications, pulmonary emphysema was manifest. In this type of tuberculosis, constitutional symptoms are few, and the local manifestations of cough, dyspnoea and wheezing dominate the clinical picture. Several of our cases had recurrent pulmonary haemorrhages in the absence of cavities. One of Sweany's (20) cases died of a pulmonary infarct consequent to thrombosis of a pulmonary vessel. Derscheid and Toussaint's (11) case died from erosion of the bronchial artery. Even in the absence of tuberculosis, haemorrhages occur in 25 per cent of all cases of emphysema recognized clinically (26). The haemorrhage usually is from the bronchial mucosa and is due to enlargement of the capillaries as an expression of collateral circulation caused by the gradual obliteration of the pulmonary capillaries in emphysema.

The relation of emphysema to tuberculous cavities and to pleural adhesions: Tuberculous cavities are often embedded in emphysematous lung (19). The lung tissue peripheral to the cavity is of necessity poorly supplied with blood vessels, the normal blood channels being intercepted by the cavity. Large emphysematous vesicles may show on the roentgenogram just outside of the cavity or they may be seen through the cavity circle if situated anteriorly or posteriorly to it. The development of pleural adhesions to the chest-wall seems to improve the nutrition of the adjoining lung by reason of collateral circulation from the intercostal arteries (27). It is exceptional to find large emphysematous vesicles under broad pleural adhesions. Extensive emphysema has been known to disappear following adhesive pleuritis (28). Often a rim of well vascularized lung may be seen between a thick-walled cavity and the chest-wall. Pathologists have marvelled at the absence of necrosis in these areas (12). The explanation lies in the collateral circulation through pleural ad-

hesions. Interlobar adhesions and pleuropericardial adhesions also furnish sources of collateral circulation (27) and interpose a barrier to the progress of tuberculosis and of emphysema.

Below the thickened interlobar fold the lung is often emphysematous and very radioluscent. This, however, is a form of complemental emphysema, provoked by the contraction of the upper lobe.

Pulmonary emphysema following therapeutic pneumothorax and thoracoplasty: Upon reëxpansion, the lung kept compressed by pneumothorax for long periods is generally found to be emphysematous. This is more likely to be so in cases with chronic pleural effusion. Lindblom (29) found these lungs to be the seat of obliterative endarteritis. The expanding lobules are often more radioluscent than the surrounding pneumothorax (30, 31). The contralateral lung also tends to become emphysematous, due to increased functional activity, but to a lesser degree than does the contralateral lung of an extensive thoracoplasty. The elevated intrapleural pressure on the pneumothorax side tends to prevent overinflation of the functioning lung. After the pneumothorax is abandoned, the intrapleural pressure sinks, and the two lungs undergo compensatory emphysema, obliged as they are to fill the vacant hemithorax. The more extensive the tuberculous involvement, the more extensive is the complemental emphysema in these cases. The contralateral lung may undergo marked dilatation and often bulges into the opposite hemithorax in the form of a mediastinal lung hernia (32).

Following thoracoplastic operations, the untreated lung enlarges; it has limited expansion, an excess of residual air, and its intrapleural pressure is raised (33); in other words, the lung becomes emphysematous. The reason for the emphysema lies in the labored breathing which these cases present, and the increased tone of the inspiratory muscles. These patients are obliged to maintain a high respiratory position in order to facilitate the circulation of blood through the lungs.

ILLUSTRATIVE CASES

Case 1: World War veteran, first examined in January, 1930, at age of 34. He complained of tiring easily. There were no abnormal physical signs in the lungs and no roentgenographic changes of active tuberculosis. In December, 1933, he was reëxamined and still presented no objective signs of tuberculosis. In the spring of 1936, he lost weight and strength rapidly. He entered the Veterans Administration Facility, Wadsworth, Kansas, where he was classified as far advanced bilateral tuberculosis. The roentgenogram of December 12,

1933 shows a single emphysematous bulla in the right apex. On the film of May 14, 1936, there is the typical mottling of progressive tuberculosis in both lungs. There are emphysematous changes in both bases and bullae in both apices. A giant bulla can be seen in the right lung between the first and third ribs anteriorly (figure 1).

The necropsy report dated June 10, 1936, reads in part as follows: "There are scattered and confluent tubercles in the upper two-thirds of both lungs. The right lung contains three air cysts, the smallest measuring 1 x 3 x 4 cm. The left lung contains a solitary cyst in the apex." (Figures 2 and 3.)

Case 2: First examined in January, 1935, at the age of 39. For two years he had been complaining of cough, shortness of breath, and pain in the left breast. The physical signs were those of asthmatic bronchitis. The sputum was negative. The roentgenograms showed evidence of fibroid tuberculosis with multiple calcifications in both lungs (figure 4) and several rings of emphysema in the left apex. He was admitted to the Veterans Administration Facility, San Fernando, California, on January 7, 1936, with a left-sided spontaneous pneumothorax. The roentgenogram (figure 5) shows increase in the mottling as well as in the emphysematous changes in both lungs.

Postmortem findings, January 29, 1936, by Dr. E. Ziegler: "Right lung is inflamed in patches; scattered throughout this lung are nodules varying in size from a pin-head to a small bean, some of them calcified. The pleura is greatly thickened and there are many fibrous adhesions on this side. The left lung is about two-thirds collapsed, the pneumothorax being posterior in situation. Anteriorly there are adhesions to the chest. The left lung presents numerous transparent bullae, fairly uniform in size, about one-fourth inch in diameter. Numerous tuberculous nodules in this lung." (Figure 6.)

As in case 1, the postmortem examination disclosed much more emphysema than was anticipated. The emphysema was more extensive on the left side. The pleural adhesions on the right side probably interfered with the progress of lung atrophy on this side.

Case 3: Spanish War veteran, 57 years old. Attack of pleurisy, left, in 1926; chronic cough since. Expectoration appeared in 1931. First examined in November, 1932. The expansion was limited on left side. The breathing was labored and wheezing. Breath-sounds were feeble over base of left lung posteriorly. Signs of cavity were present above the second rib anteriorly on left side; musical râles were scattered over both lungs. On two occasions the man expectorated branching pieces of stone, the size of a grain of wheat.

The roentgenograms showed bilateral tuberculosis, with a large cavity in the left upper lobe. Many calcareous nodules were seen in left lung, one of

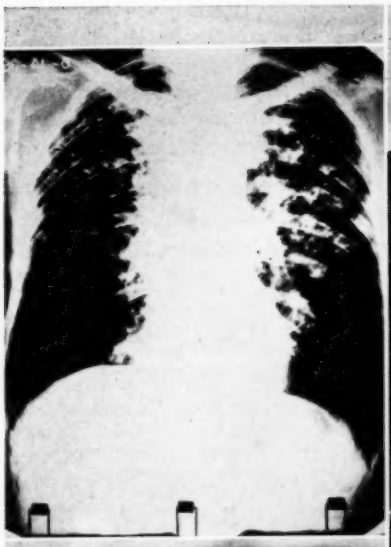

FIG. 1

FIG. 2

FIG. 3

FIG. 6

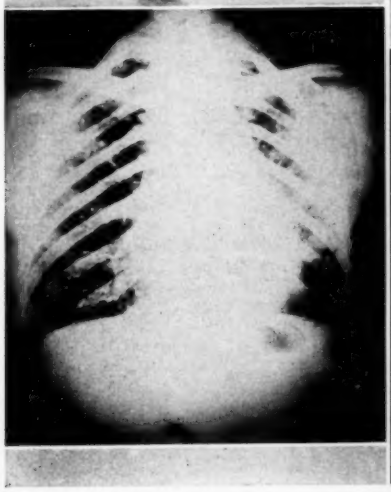

FIG. 4

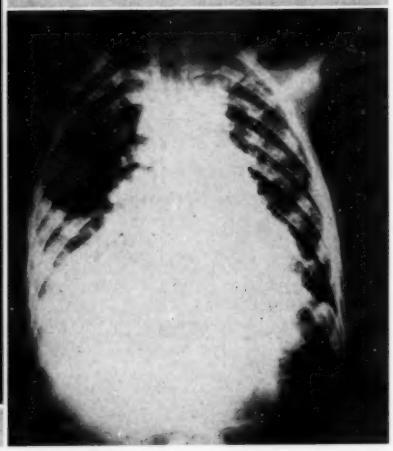

FIG. 5

them in relation to the lower lobe bronchus. The left lower lobe was emphysematous and did not deflate on expiration (figures 7 and 8).

In this case it is believed that there was a stricture in the bronchus of the left lower lobe, caused by an ulcerative calcareous lymph node. The stricture acted in a ball-valve manner and led to obstructive emphysema.

Case 4: World War veteran, age 44. Poorly developed and subject to bronchitis and heart trouble since childhood. Was accepted into the army for limited service only, by reason of valvular insufficiency and chronic bronchitis. On October 28, 1937, he suddenly developed spontaneous pneumothorax on the right side. Upon rest in bed the pain in the chest and the dyspnoea subsided, but on November 3 the pain returned, the dyspnoea became severe, and there was cyanosis. He was admitted to the Veterans Administration Facility at Batavia, New York, on November 4, with symptoms of spontaneous pneumothorax and subcutaneous emphysema. He required repeated aspirations of air from the right pleural cavity, as there were attacks of recurrent pneumothorax. The right lung finally reëxpanded in about six weeks. The heart showed no murmurs, but had the X-ray appearance of *cor pulmonale*. The left lung showed physical signs of atelectasis of the lower lobe, absent breath-sounds, and coarse moist râles.

The roentgenogram of November 4, 1937 (figure 9) shows a large pneumothorax on the right side. The three lobes can be identified. The middle lobe is very transparent and on the original film shows many rings of emphysema. The upper lobe bulges into the left chest to form a mediastinal hernia. Emphysematous changes can be seen in this hernia. The left lung is distinctly emphysematous at its base. In the upper half there are several fibrous nodules. Between the seventh and ninth ribs posteriorly there is a large comma-shaped calcified pass, partly obscured by the heart shadow; it is in relation with the lower lobe bronchus. The trachea is displaced to the left and the large bronchi are visualized. The heart is enlarged and distorted. The enlargement involves the right ventricle, the conus, and the pulmonary arteries.

The man had suffered an extensive tuberculous infection in childhood, with atelectasis of the left lower lobe. There developed emphysema of both lungs, the right lung herniating into the left hemithorax. There were signs of em-

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FIG. 1. Case 1. June 10, 1936. Changes typical of tuberculosis in both lungs. Many annular shadows of emphysema; giant bulla between first and third ribs on right side.

FIG. 2. Case 1. Photograph of left lung. Note large apical bulla.

FIG. 3. Same case. The apical bulla incised.

FIG. 4. Case 2. January 10, 1935. Many fibrous and calcareous nodules in both lungs. Mottling in left midlung. Circles of emphysema in apex and first interspace on left side.

FIG. 5. Case 2. January 28, 1936. Right base mottled. The emphysematous changes are more pronounced in left lung; some bullae can be seen in the right apex.

FIG. 6. Case 2. Photograph of left lung. Emphysematous bullae in both lobes. The largest bullae are in the apex.

FIG. 7

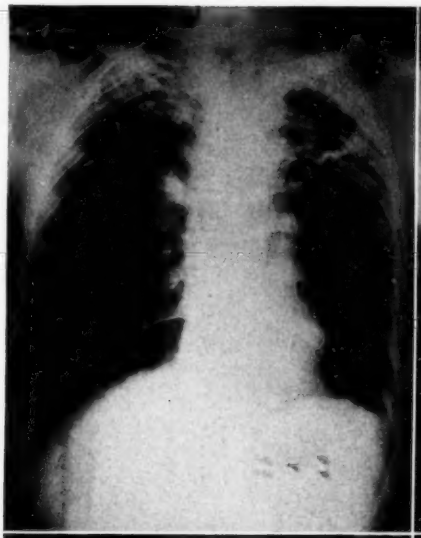

FIG. 8

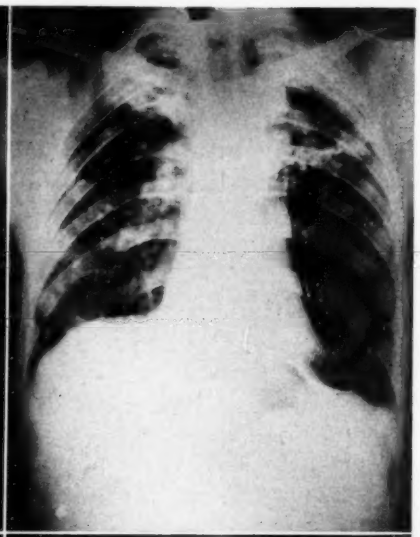

FIG. 9

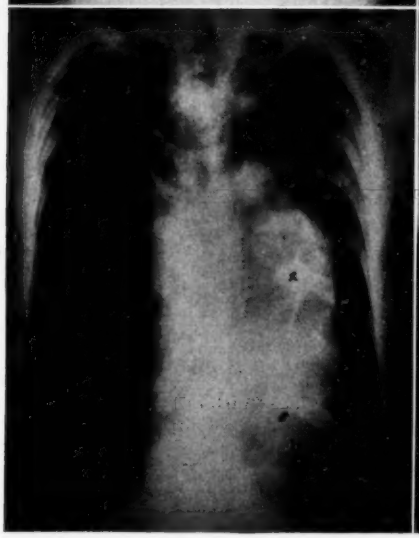

FIG. 10

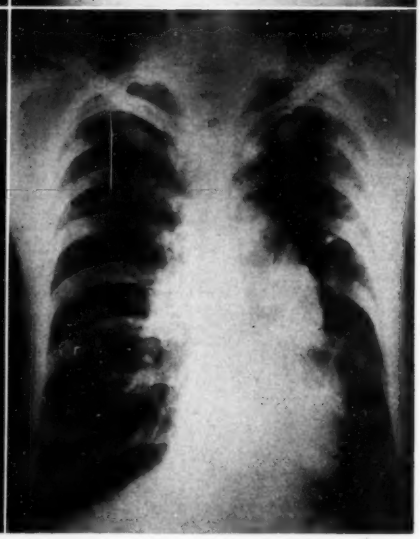

FIG. 7. Case 3. Film taken in inspiration. Obstructive emphysema, left lower lobe. See text.

FIG. 8. Case 3. Film taken in expiration at same sitting as fig. 8. The right base has become deflated but not the left. The heart is displaced to the right.

FIG. 9. Case 4. November 4, 1937. Incomplete pneumothorax, right. Right upper lobe adherent; its mediastinal portion bulges into left hemithorax. The left upper lobe shows emphysema at its base and changes of fibrous tuberculosis above the third rib. The left lower lobe is atelectatic, *cor pulmonale*. (1) Mediastinal border of left upper lobe. (2) Calcified node in relation to left bronchus. (3) Atelectatic left lower lobe. (4) Left border of heart.

FIG. 10. Case 4. Right lung has reëxpanded. Its mediastinal hernia persists. Changes of emphysema in both lung bases.

barrassment of the right heart. The recurrence of the pneumothorax and the severe symptoms of the partial pneumothorax are attributable to the labored breathing, caused by the inadequate heart and left lung.

SUMMARY AND CONCLUSIONS

1. In tuberculosis, emphysema is usually vascular in origin, being caused by atherosclerosis, endarteritis or thrombosis, involving the pulmonary or bronchial arteries. The emphysema is often complemental in nature, when the lung is obliged to stretch and fill space created in the chest by contraction or atelectasis of diseased lobules. The complemental emphysema does not differ from essential emphysema, either histologically or functionally.

Contributing factors are the coughing spells and labored breathing in tuberculosis; also, the descent of the diaphragm and the impairment of the heart in pulmonary tuberculosis.

2. Emphysema occurs in all forms of tuberculosis, but is more extensive in the chronic forms. In the form with scattered fibrous and calcareous nodules it is most extensive and may cause physical and X-ray signs which obscure the symptoms of tuberculosis.

3. The apical bullae so commonly seen postmortem depend on tuberculous scars. They are the usual cause of benign spontaneous pneumothorax.

4. Emphysematous lung usually surrounds tuberculous cavities.

5. Emphysema is not common in the immediate vicinity of thickened pleura. Pleural adhesions, by virtue of their collateral circulation, offer a barrier to the tuberculous process, as well as to lung atrophy (emphysema).

6. Following the abandonment of a therapeutic pneumothorax, both lungs usually develop emphysema. Following a thoracoplastic operation the contralateral lung also undergoes changes of emphysema.

It is desired to acknowledge the coöperation of the Research Subdivision, Medical and Hospital Service of the United States Veterans Administration, in this and other studies. The following Medical Officers assisted in compiling the data for this report: Dr. P. A. Waters, Batavia, New York, Dr. L. J. Bernard, San Francisco, California, and Dr. Robert M. Fullwider, Wadsworth, Kansas.

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TUBERCULOSIS OF THE THYROID GLAND

HENRY W. LOURIA[1] AND MILTON R. LOURIA[1]

Tuberculosis of the thyroid gland occurring as isolated organ tuberculosis without demonstrable tuberculous involvement in other parts of the body is a distinctly rare condition.

Smith and Leech (1), in 1928, reviewed the histological study of 1,500 goitres operatively removed at the Lahey Clinic and found evidence of tuberculosis in three instances. In these patients there was no evidence of tuberculosis elsewhere in the body. In the first of these cases, sections of the gland showed small miliary areas suggesting tuberculosis. There was no caseation and no giant cells were seen. The second case presented the picture of chronic thyroiditis; epithelial cells and giant cells were noted, and sections stained with carbolfuchsin showed beaded microörganisms presenting the morphological appearance of tubercle bacilli. The third case presented a histological picture similar to the second.

Coller and Huggins (2), in 1926, reported five cases of tuberculous involvement of the thyroid gland in a series of 1,200 cases of thyroid disease operatively treated. One of these was an adenomatous goitre with areas of caseating tuberculosis. Two were adenomatous goitres with miliary tubercles. The remaining two cases showed the histological picture of exophthalmic goitre with scattered miliary tubercles in the gland.

Seed (3) states that he failed to find a single instance of gross or microscopical evidence of tuberculosis in a series of 1,400 goitres.

Even in individuals dying of tuberculosis, the incidence of involvement of the thyroid gland is low. There has been a good deal of discussion of the relative immunity of the thyroid gland to infection with the tubercle bacillus. At the present time experimental evidence to demonstrate this point is not conclusive.

PATHOGENESIS

There seems to be no good reason to consider tuberculosis of the thyroid gland as differing in any essential respect from isolated organ tuber-

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culosis elsewhere in the body. The apparent route of infection is through the blood-stream. Whether or not the tubercle bacilli reach the thyroid gland during the stage of dissemination following the primary infection, or whether the bacilli are subsequently released from a focus elsewhere in the body, is impossible to state with any certainty. The entire question of localization of the tubercle bacillus in the thyroid, rather than in the kidney or in a joint, would seem to be a matter of chance. Once infection of the gland has taken place, the local pathological changes would seem to be dependent upon the number of bacilli, the virulence of the microörganisms and the allergic state of the host. Thus, one may find isolated tubercles, extensive caseation, or a marked fibrous tissue reaction. In other words, the variety of pathological changes that have been noted in the thyroid gland are similar to those seen in the lung.

In connection with tuberculosis of the thyroid gland, the question arises whether preceding changes in the gland, such as adenomata or exophthalmic goitre, predispose toward the development of tuberculous infection. In other words, will tubercle formation progress more readily in a thyroid gland which has been previously altered by a pathological process than in a normal gland? At present there is no experimental or clinical evidence to decide this point.

CLINICAL DIAGNOSIS

There are no criteria on which a definite preoperative diagnosis of tuberculous involvement of the thyroid gland can be made, especially in the absence of active tuberculosis elsewhere in the body. Even the presence of active pulmonary or extrapulmonary tuberculosis, or of a positive tuberculin test, is hardly sufficient reason to state that a coexisting goitre is tuberculous in character. The symptoms and signs may be those of a nontoxic adenoma of the thyroid, a Riedl's struma, or Basedow's disease. The basal metabolic rate may be normal or elevated, and the signs of toxic hyperthyroidism may or may not be present.

TREATMENT

To discuss the treatment of tuberculosis of the thyroid gland would imply that accurate diagnosis had been made before the institution of appropriate therapeutic measures. As diagnosis is not possible until operative removal of the gland has been carried out, one can only mention the results of treatment as measured by the outcome in operated

cases. In the reported instances of tuberculosis of the thyroid gland, subtotal thyroidectomy in the usual manner was carried out. Wound healing and convalescence have not been noted to differ in any respect from the ordinary. No instance has been reported of a draining sinus following thyroidectomy in these cases.

HISTOLOGICAL DIAGNOSIS

The mere presence of groups of epithelioid cells and giant cells in the thyroid gland does not constitute adequate proof of a tuberculous involvement of the gland. Jaffé (4), in 1930, discussed this question and reported four instances in a group of 300 thyroid glands operatively removed in which nodular structures were found composed of epithelioid cells and giant cells which strongly resembled tubercles. No tubercle bacilli were found in any of these cases although an extensive search was made for the microörganisms. It was Jaffé's belief that the histological changes in these cases represented the end result of noninfectious focal involutional changes. A painstaking study of the sections suggested to him that the epithelioid and giant cells had their origin in the follicular epithelium. Jaffé emphasized the fact that, for diagnostic purposes, the demonstration of bacilli is of prime importance, although admitting the fact that this is often very difficult even in definitely tuberculous tissue. Moreover, in sections of the thyroid gland stained for acid-fast microorganisms, one must be particularly careful in differentiating bacilli from small linear collections of colloid which may retain the fuchsin stain and thus closely resemble acid-fast bacilli.

For undoubted proof of the existence of tuberculosis of the thyroid gland, one would therefore expect characteristic histological evidence, substantiated by the demonstration of tubercle bacilli on culture of the tissue or through guinea-pig inoculation. In the case reported below, the histological appearance of the gland was tuberculous in character, and sections stained by the Ziehl-Neelsen method showed groups of microörganisms with the typical morphological appearance of the tubercle bacillus. However, at the time these findings were completed, no fresh tissue was available for either culture or guinea-pig inoculation.

Case Report

M. W., female, married, age 31 years, appeared for examination on August 11, 1937, with a complaint of a mass in the front of the neck of two months' duration. The mass had been slowly increasing in size. The patient had

been nervous for seven years and had had frequent attacks of palpitation. There had been no loss of weight, and no sweats. Her appetite was good.

The family history was negative for tuberculosis and thyroid disease. The mother died of heart trouble at the age of 58. The father was living and well at 61. The patient had three sisters and one brother, all of whom were living and well. No siblings had died.

The patient had been married for eight years. She had a miscarriage five and a half years ago. Fifteen months ago she had a normal delivery at full term; there were no complications of pregnancy. The patient's husband and one child were alive and well. There had been no severe illnesses in the past and no operations. Three years ago the patient injured her lower back in an automobile accident and a cast was applied to the lumbar spine for forty days. Since that time there had been no symptoms referable to the area of injury. There were no symptoms of disturbance of the gastrointestinal, cardiac, respiratory or genitourinary systems.

Physical examination showed a well developed and well nourished white female adult. Weight 108 pounds. Blood pressure 110/70. Temperature 98.6°F. Pulse 104. There was slight exophthalmos. The thyroid gland was obviously enlarged and firm. No nodules were palpable. The gland was slightly tender. The lungs were clear to percussion and auscultation. The heart was not enlarged. No murmurs were heard. There was a fine tremor of the fingers. Otherwise, the physical examination was essentially negative.

Laboratory data: Haemoglobin 78 per cent; red blood cells 3,600,000; white blood cells 11,800; polymorphonuclears 69 per cent; lymphocytes 30 per cent; mononuclears 1 per cent. The specific gravity of the urine was 1.012; no albumin; no sugar.

Basal metabolic rate was plus 39.

X-ray examination of the chest revealed no evidence of pulmonary infiltration. Heart and aorta were within normal limits.

A clinical diagnosis was made of probable Riedl's struma with hyperthyroidism, and the patient was admitted to the Jewish Hospital of Brooklyn for operation.

Lugol's solution, 10 drops every four hours, was administered preoperatively. On August 23, 1937, under avertin anaesthesia, a subtotal thyroidectomy was performed (H.W.L.) in the usual manner. At operation the thyroid gland was found to be irregularly enlarged, hard, yellowish-white in color, friable and relatively avascular. The impression at the time of operation was that of chronic thyroiditis.

Pathological report (Dr. David Grayzel): The specimen consists of two portions of firm thyroid tissue, 5 by 2.5 by 2 cm. and 3.5 by 2.5 by 2 cm., together weighing 15 gm. Part of the external surface is smooth and glistening. The remainder is rough. The cut surfaces are pale brown, streaked

with gray. Microscopical studies show a variegated picture; in places there are small groups of acini varying somewhat in size and shape, lined by flat or cuboidal epithelium, and containing pink staining colloid. In other places the acini are surrounded by abundant dense hyalinized fibrous tissue. About some of the acini are multinucleated giant cells. Some of these cells form fine tuberculous structures composed of radially arranged epithelioid cells and collared by small round cells. Some of the tubercles are confluent. Stained by the Ziehl-Neelsen method, acid-fast microörganisms are seen.

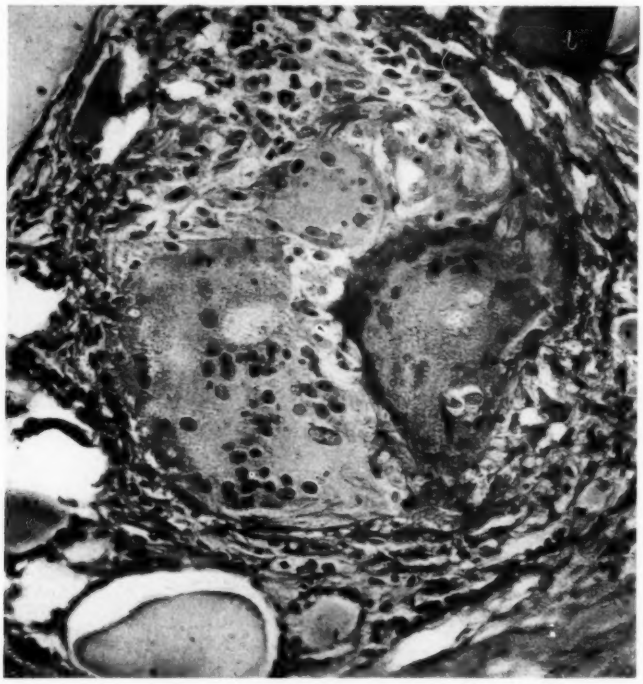

FIG. 1. High power view of typical giant cells

Pathological diagnosis: Thyroid gland with thyroiditis and tuberculosis.

The patient was discharged on the fourth day after operation. The wound was completely healed within two weeks after operation.

When the report of tuberculosis of the thyroid gland was received, the patient was recalled for further study. The urine study for tubercle bacilli was negative. An X-ray film of the abdomen was taken for evidences of calcified foci in the retroperitoneal or mesenteric nodes and in the spleen, but no evidences of such calcific foci were disclosed. A Mantoux test was two plus.

SUMMARY

A case of tuberculosis of the thyroid gland is reported which presented the clinical picture of a thyroiditis with hyperthyroidism. Subsequent study revealed a positive tuberculin reaction, but no evidence of pulmonary or renal tuberculosis, and no evidence of tuberculous foci in the spleen or abdominal nodes.

CONCLUSIONS

1. Isolated organ tuberculosis of the thyroid gland is a rare condition.
2. The pathogenesis of this condition is probably through haematogenous infection.
3. There are no positive criteria on which the preoperative diagnosis of tuberculosis of the thyroid gland can be made.
4. Tuberculosis of the thyroid gland may be associated with clinical evidence of hyperthyroidism.
5. The treatment of choice is subtotal thyroidectomy.
6. Wound healing and convalescence are not hindered by the tuberculous foci in the gland.
7. The only absolute diagnostic criterion is the demonstration of characteristic tuberculous pathology together with acid-fast microörganisms in the excised gland. For a complete diagnosis, culture of the bacilli or guinea-pig inoculation should be carried out.

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UNUSUAL MYCOBACTERIAL INFECTIONS[1]

GUSTAVE FREEMAN

This paper describes a variety of associated bodies that occurred together with acid-fast bacilli in two patients. The clinical picture in the patients from whom these microörganisms were obtained was that of recurring abscesses of the subcutaneous tissues and viscera. Draining sinuses often remained at the sites of ruptured abscesses.

The patients had been under observation in this clinic for two and a half and five years, respectively, before any satisfactory evidence of aetiology was obtained.

Case 1: A woman, 43, came to the clinic October 11, 1934. At 16 an abscessed tooth was pulled. Immediately, the side of the face and neck became swollen and tender. The lymph nodes of the neck were excised. At the age of 36 another tooth was extracted. A similar episode occurred. Three months later a third tooth was pulled. This time not only the face and neck became inflamed but the axillary lymph nodes were also affected and pus began to drain through a sinus tract. Since then (five years ago) crops of subcutaneous abscesses appeared on all parts of the body except the head. In addition there have been recurring attacks of redness, swelling and tenderness of the joints. Some of the subcutaneous lesions persisted as draining sinuses, others became superficial, flat ulcerations of the skin, while many disappeared without breaking through to the surface. Several of the lesions arose deep in the subcutaneous tissue and slowly became fluctuant. When large, deep abscesses were aspirated, greenish-yellow, bloody pus was obtained. With the centres emtied of their fluid contents umbilicated areas remained due to the firm, raised, inflammatory tissue that formed the walls of the abscesses. The spleen was large. Fever was seldom present. The patient gained weight while at rest in bed. She was discharged after eighteen months. A month later she was readmitted because of pleural pain. The entire right pulmonary field was obscured on X-ray by an opaque shadow. Previously there was evidence only of enlarged hilar lymph nodes, and later an elevated diaphragm with an increasing shadow in the base of the right lung. The shadow disappeared within a week. It was thought that an exudate had penetrated through the diaphragm into the pleural cavity from the liver. The patient gradually improved. Most of

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the lesions dried up and the disease was quiescent. After five months of remission, in December, 1937, she developed another large abscess on the right shoulder.

Biopsies: The biopsies were made from the skin. The epithelium was well preserved except for papillary hyperplasia of the margins of ulceration. The dermal fibrous connective tissue was infiltrated with mononuclear leucocytes to a variable degree. In the deeper portions of the cutaneous connective tissue, adipose layer and muscular tissue, the inflammatory reaction was more marked. Here necrotic areas were filled with polymorphonuclear leucocytes, mononuclear cells and haemorrhage. Here and there were groups of epithelioid cells. No tubercles or giant cells were seen. The picture was one of acute and chronic nonspecific inflammatory reaction of the skin and subcutaneous tissue.

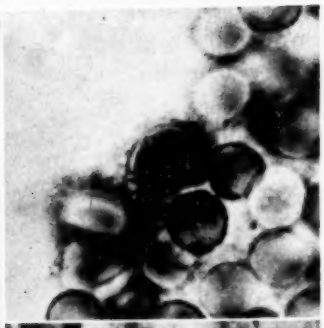
Recent study with new preparations made from old fixed material from skin biopsies revealed two interesting elements. Scattered among the red cells in an area of fresh haemorrhage were seen deep pink, yeast-like bodies. These appeared to be encapsulated and were somewhat larger than red cells. These were demonstrable in haematoxylin and eosin (figure 1) and Gram-Weigert preparations (figure 2). The bodies were not acid-fast. A second element, discovered in an acid-fast preparation, consisted of minute acid-fast granules that occurred rarely in the cytoplasm of mononuclear macrophages. Only two such cells were found; the latter was of special interest because it was the only direct evidence for the presence of acid-fast material in either of the two patients.

In fresh, unstained pus preparations globoid, doubly contoured, granular, yeast-like bodies were occasionally seen floating along with the red cells. These bodies ruptured and permitted a flow of granules. The empty capsules were indistinguishable from red cells. Before dispersing their contents they were morphologically identical with the bodies seen in figures 1 and 2.

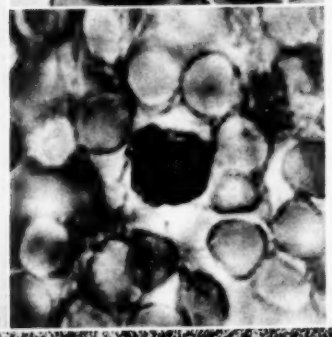
On January 17, 1936, February 4, 1936, and September 30, 1936, blood-tinged, greenish-yellow pus was aspirated from subcutaneous abscesses.

Animal inoculation: With the material from each of the first two aspirations, the brain of a guinea pig was inoculated. In each case the animal became moribund in eight weeks. Only the brains showed evidence of infection. The lesions in both brains were similar; no acid-fast microorganisms were found in sections of the first animal, but were seen in

G. 1



G. 2



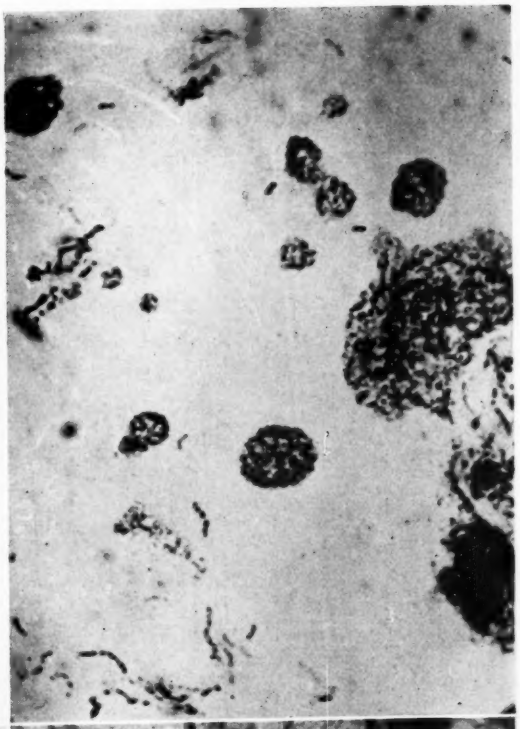


FIG 3

IG. 4

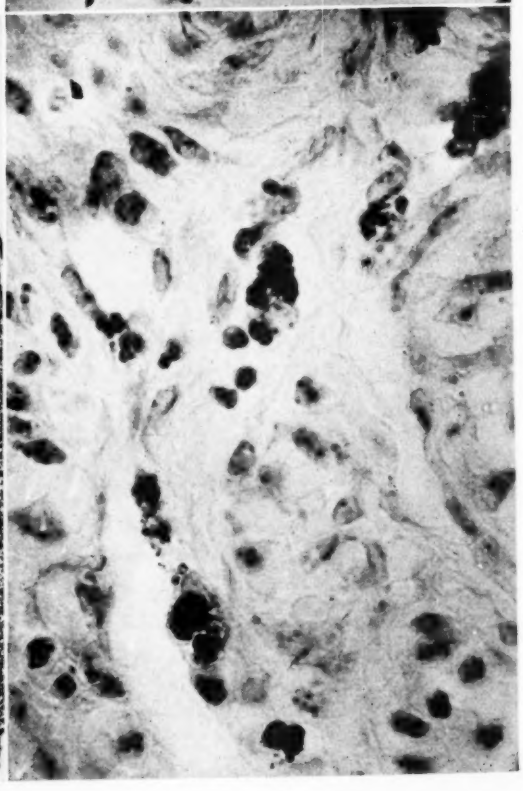


FIG. 5

the second. The material from the third aspiration was inoculated both intracerebrally and intratesticularly into a guinea pig. This animal was killed while moribund six weeks after inoculation. Large lesions were found in the brain, testis, inguinal lymph node, liver, spleen and lungs. The brain was removed aseptically from this animal and was used for further inoculations.

The infection was passed through six guinea pigs in series without loss of virulence. Ground-up liver was inoculated intratesticularly each time. It was possible to infect animals by subcutaneous injection into the groin as well. The infection was always fatal in guinea pigs.

Cultural Characteristics: Many unsuccessful attempts have been made to obtain a growth from pus on various media. When guinea pigs were infected, material from the animals was used likewise.

The cultures were kept until the agar was dry. About a week after inoculation with animal tissue, minute, barely visible blebs appeared on the dry sheep-blood agar in the line of inoculation. When these minute "blisters" were examined microscopically acid-fast bacilli were found in large numbers. Subcultures were made on Petroff's and Löwenstein's media although no growth was obtained when pus or animal tissue was planted directly on these media. Cream colored colonies resembling those of typical human or bovine tubercle bacilli appeared approximately on the fifth day. A fairly luxuriant growth was obtained on both kinds of media but more so on Löwenstein agar. The microörganisms continued to grow well after ten transfers. As the colonies grew older the pale yellow changed to a deep yellow and then to a golden-brown.

Smears showed well beaded, acid-fast bacilli side by side with morphologically similar non-acid-fast bacilli. In young cultures the non-acid-fast variety predominated but the ratio changed as the cultures

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FIG. 1. Encapsulated, granular, yeast-like body lying among red cells in skin of first case. The body stains deep pink. Haematoxylin and eosin. × 2150

FIG. 2. Same kind of body as that seen in fig. 1. The body stains pink and the red cells stain yellow. Gram-Weigert. × 2150

FIG. 3. Smear from a "lavender" colony grown on Petroff's medium from infected guinea pig tissue from the first case. The round, granular bodies are deep red but contain occasional large black granules. The same is true of the beaded bacilli. Carbolfuchsin and methylene-blue. × 1532

FIG. 4. Masses of epithelioid cells in tubercle-like formation in spleen of guinea pig infected with pus from the first case. Haematoxylin and eosin. × 53

FIG. 5. Phagocytized masses of material that vary in size, shape, and staining property. They vary from deep red to faint pink. Many do not take the stain and remain golden-yellow. Carbolfuchsin and methylene-blue. × 900

grew older. These smears resembled others made from known human and bovine strains of the same age. Smears of old lavender colonies had, besides ordinary appearing acid-fast bacilli, large round bodies that consisted of a thin acid-fast membrane enclosing minute acid-fast granules (figure 3).

In one instance, acid-fast bacilli were cultured on a blood agar plate directly from the pus of a new abscess from the patient. Glycerine broth was inoculated. The microörganisms tended to sink so that a surface growth was not obtained but a slow growth was observed in the broth. After six weeks a preparation analogous to Old Tuberculin was made from the scanty growth by the method of Koch (1). The concentration of this "tuberculin" was, therefore, considerably less than that obtainable in human tuberculin. The broth culture contained viable microörganisms. Uninoculated broth from the same batch was treated in the same manner for use as a control.

Pathogenicity: Injections of 1.0 mg. of the agar culture were made into the groins of a guinea pig, a rabbit, a chicken, and a frog. After thirteen weeks the latter three appeared well but were killed. The guinea pig died with infection in three weeks. The rabbit was infected but had only a few scattered gross lesions in the viscera. The chicken and the frog were not affected.

Guinea-pig lesions: In the guinea pigs inoculated intratesticularly, the gross character of the lesions was similar to that seen in infections with a human strain of tubercle bacilli. The organs involved were the inoculated testis, the regional inguinal lymph nodes, the spleen, the liver, the lungs, and occasionally the adrenals. The distribution was that of a disseminated spread through the blood-stream.

Microscopically, the earliest lesion was a small accumulation of epithelioid cells. These groups increased in size and gave the appearance seen in figure 4. The structure of the surrounding tissue was seldom altered by the masses of invading cells. In the liver, the hepatic cells were replaced by groups of epithelioid cells, and in the spleen the germinal centres of the Malphigian bodies were similarly replaced. As these lesions became more extensive, caseous necrosis began to appear in their centres. This stage was invariably reached at the sites of inoculation and from time to time in other organs.

No giant cells were found in the animals inoculated with pus or in the first few subsequent passages, but later a tendency towards coalescence of epithelioid cells was noted and finally an occasional giant cell was

seen. The peripheral bands of lymphocytes usually seen around tubercles were scanty. The microscopical structure of the huge spleen of a heavily infected animal consisted almost entirely of spongy pulp engorged with blood. This was due to active hyperaemia and haemorrhage. The lesions were largely proliferative and granulomatous in character. Necrosis was not prominent and fibrosis was practically absent.

In animals infected with microörganisms from a culture the lesions resembled tuberculosis more closely than in those infected with pus from the patient. Caseous necrosis was more widespread and giant cells appeared more often.

The lesions in the rabbit were less extensive but had the same histological appearance as those in the guinea pig.

Bodies associated with acid-fast bacilli in guinea pigs: The long search for the aetiology of the infection and the peculiar course of the disease indicated an uncommon microörganism.

Acid-fast bacilli were found in all animals that were inoculated with either pus, infected animal tissue or cultures. The number of bacilli in the tissue varied directly with the size of the lesion. Besides the acid-fast bacilli, non-acid-fast, diphtheroid-like microörganisms were present from time to time in the sections where practically no pathological change was detected. These microörganisms took gentian-violet poorly.

All infected guinea pigs contained large amounts of phagocytized golden-yellow material that did not stain with haematoxylin or eosin. It was found in greatest quantity in the spleen and around the sites of inoculation. This material was usually globoid in shape and homogeneous in color. These bodies occurred individually and in clusters. They varied in size from small granules to masses as large as red cells. In the testes of animals inoculated with pus most of this material retained the carbolfuchsin avidly and gave the appearance seen in figure 5. The affinity for the stain was not constant so that these bodies varied in color from deep red to faint pink. Many were unstained golden-yellow structures. Often the centres did not stain so that the bodies appeared like clusters of bubbles. This material was found around, rather than in, caseous areas. One deeply stained body of this kind appeared distinctly to be made up of closely packed bacillary forms whereas the others were homogeneous. Here and there in the pigs inoculated with pus from the patient were found large golden-yellow bodies that consisted of a capsule with enclosed granules. These were rarely encountered.

Skin tests: The patient gave unusually violent skin reactions to intracutaneous injections with human, bovine and avian tuberculin. This was likewise true when antigens made from pyogenic microörganisms were used. Due to her peculiar sensitivity it was difficult to evaluate intracutaneous tests.

Three normal persons who gave negative skin reactions with human Old Tuberculin in a dilution of 1:10,000 did not react to the "Old Tuberculin" made from the microörganism under discussion. A patient with a strong family history of tuberculosis and a clinical diagnosis of lupus erythematosis, who gave a negative reaction to human Old Tuberculin in a dilution of 1:1,000, gave a positive test to the same dilution with the "Old Tuberculin" made from the isolated microörganism. In each instance 0.1 cc. was given intracutaneously.

Infected guinea pigs always had negative skin tests to the following: the new "Old Tuberculin," bovine and avian Old Tuberculin. Guinea pigs infected with avian tubercle bacilli were negative also. However, guinea pigs infected with bovine bacilli gave positive skin reactions. The rabbit and chicken did not react to any of the tuberculins used above.

The isolation of a pathogenic microörganism from the first patient prompted reinvestigation in the second case because of the clinical similarity between the two.

Case 2: A woman, 43, first came to the clinic in February, 1933. For about eighteen years the patient had a nonproductive cough. Five months prior to her appearance at the clinic she began to raise sputum, lose weight, and to suffer epigastric pain. A firm, nonfluctuant mass about 6 cm. in diameter appeared in the left supraclavicular fossa. The mass was biopsied and, soon after, pus began to appear in the urine. X-ray films of the chest consistently showed a mediastinal shadow. Late in 1933 the sinus that occurred at the site of biopsy was still draining. New abscesses appeared deep in the wall of the thorax and new pulmonary shadows were evident. The following year an abscess under a breast began to drain. In 1935 an inflammatory mass de-

FIG. 6. Macrophages in skin of second case. The smaller cell is filled with large, golden-yellow granules that surround the nucleus. The elongated cell that is partially out of focus contains smaller granules that stain greenish-yellow. Haematoxylin and eosin. × 2132

FIG. 7. Macrophage, like larger one in fig. 6, containing smaller type granules. These take deep blue stain. Carbolfuchsin and methylene-blue. × 2665

FIG. 8. Golden-yellow granular body in liver of guinea pig from second case. Occasional granules are large and black. Carbolfuchsin and methylene-blue. × 2150

FIG. 9. Golden-yellow body from same preparation as fig. 8. This one contains bacillary rather than granular material. Carbolfuchsin and methylene-blue. × 2150

FIG. 6

FIG. 7

FIG. 8

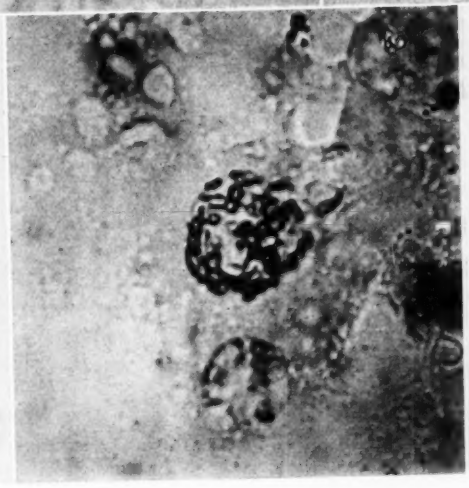

FIG. 9

veloped and subsided in the left lumbosacral region. An empyema with osteomyelitis of a rib and a perinephritic abscess were drained. In 1936 episcleritis developed. The patient was afebrile except for the periods during development of large abscesses. At the time of the writing the patient's general condition permits her to do her housework. However, abscesses continue to appear, break down spontaneously, and discharge through the skin.

Four biopsies were made of the skin and subcutaneous tissues. Here, like in the first case, the material presented a picture of acute and chronic inflammatory reaction of a nonspecific nature. However, in all haematoxylin and eosin sections were found large macrophages whose cytoplasms were filled with golden-yellow granules (figure 6). The granules were divided roughly into two sizes. Individual macrophages contained either the larger or the smaller type, but not both. The smaller granules had a faint greenish tint. Stained with carbolfuchsin and methylene-blue, the larger ones took a greenish-yellow color while the smaller granules, like those in figure 7, were deep blue. No acid-fast material was seen. Bodies resembling those in figures 1 and 2 occurred in some of the sections.

Five-tenths cc. of pus was obtained from a fresh abscess. This was inoculated into the testis of a guinea pig on September 17, 1937. The animal died twelve weeks later with large disseminated lesions in the testis, inguinal lymph node, liver, spleen and lungs. The discrete and confluent, firm, yellow lesions closely resembled those in animals inoculated with material from the previous case. Thus far, by passage of animal tissue in guinea pigs, there has not been a change in virulence.

Sheep blood, Petroff's and Löwenstein's media were inoculated with infected guinea-pig tissue. A growth was obtained on the sheep blood and Löwenstein's medium resembling that from the first case. The only apparent difference between the two microörganisms was the staining property for carbolfuchsin. Many of the bacilli from the second case did not take the stain but remained golden-yellow.

Here again, in guinea pigs the lesion was essentially granulomatous. The histological structure resembled that in the animals of the first case; giant cells were not seen but caseous necrosis occurred in sites where the infection was heavy.

Sections made from the liver of the guinea pig inoculated with pus from the patient contained the striking pictures seen in figures 8 and 9. Besides the acid-fast bacilli and golden-yellow rods previously described, numerous golden-yellow bodies were present ranging in size from twice

that of a staphylococcus to the size of a small lymphocyte. The smaller ones were homogeneous, disc-like bodies, indistinguishable from similar material described in the pigs from the first patient. Those that approached the size of a red cell had distinct capsules and were filled with golden-yellow granules (figure 8). In the largest ones the granular structures gave way to bacillary bodies that were arranged in whorls concentric with the limiting membranes (figure 9). Occasionally the membrane was seen to be ruptured. These bodies either were free in the tissue or lay within the cytoplasms of macrophages. The testes contained bodies like those seen in figure 5.

The patient gave positive skin reactions to human Old Tuberculin and to the "tuberculin" made from the microörganism isolated from the first patient.

DISCUSSION

Many questions arise out of this accumulation of observations. It seems justifiable to accept the acid-fast bacillus recovered both from the first patient studied and from the animals inoculated with material from the patient as the cause of the disease in that individual. The pathological changes in guinea pigs have been the same whether the pigs were inoculated with pus from either of the two patients studied, with a pure culture of the microörganisms recovered from guinea pigs that were infected with pus from either patient, or with tissue of infected guinea pigs.

No guinea pigs developed spontaneous infections of a similar nature during the two years of this investigation. Also it is noteworthy that the first two animals were inoculated intracerebrally and died of lesions that were confined to the brains and meninges.

In view of the clinical similarity between the two patients studied here and the common finding of an acid-fast bacillus, it is likely that these patients have identical or closely related diseases. Since the opportunity has not arisen for culturing pus directly from the second patient it is not absolutely proved that the microörganism isolated from her is responsible for her disease.

Is there any correlation among the diverse elements discovered in the individual cases, the guinea pigs and the cultures? The bodies seen in figures 1 and 2 occur in biopsies from both patients. Acid-fast and nonstaining material represented by figure 5 is found in guinea pigs from both patients. The round granular bodies seen in figure 3 are almost

identical morphologically with the one pictured in figure 8. The former is acid-fast and occurs together with acid-fast bacilli in an old culture from the first case. The latter is one of many found in guinea pigs infected from the second case. However, these are either very faintly acid-fast or not at all. The unstained ones are golden-yellow. Figures 8 and 9, made from the same slide, demonstrate apparently related bodies. They are identical except that those represented by figure 9 are somewhat larger and contain bacillary rather than granular inclusions. The bodies shown in figures 8 and 9 appear frequently to lie within macrophages.

The material seen in figure 5 appears to be engulfed almost exclusively by macrophages. Figures 6 and 7 represent large mononuclear leucocytes that are packed with granules. The difference between the granules seen in figures 6 and 8 is that in the former the golden-yellow granules fill the cytoplasm of each cell whereas in the latter instance the granules lie within a golden-yellow capsule giving the appearance of a circumscribed structure. It may be that the encapsulated appearance is given by cytoplasmic vacuoles that contain the granules. Maximow described a similar fate for tubercle bacilli in tissue cultures (2).

In all guinea pigs inoculated intratesticularly and in all but one inoculated intracerebrally, acid-fast bacilli were found in the tissues.

The microörganisms recovered from both patients fall into the genus *Mycobacterium*. The presence of bodies (figure 9) resembling "globi" (3) and the variability with which the bacilli and associated bodies retain the acid-fast stain relate the microörganisms to the leprosy bacillus of Hansen. However, their pathogenicity relates them more closely to the human tubercle bacillus. The atypical histological picture produced in guinea pigs clearly distinguishes them from the usual tubercle bacillus.

The lesion seen in figure 4, which resembles those of Böeck's sarcoid and the positive skin reaction in a patient with a diagnosis of lupus erythematosis, may be of some significance in the problem of noncaseating tuberculosis which currently is receiving considerable attention (4, 5). An interpretation at present is unwarranted.

The marked hypersensitivity demonstrated by the first patient indicates a peculiarity of the host. It is possible that the host alone is responsible for the change of a relatively ordinary tubercle bacillus into microörganisms like those under discussion. After several passages in animals, using material from the first case, bizarre elements tend to disappear and an occasional giant cell appears in the tissues suggesting a

tendency on the part of the microörganism to create a more familiar kind of acid-fast infection.

The part played by the non-acid-fast diphtheroid-like bacilli is obscure. Mellon and Beinhauer (6) have recently discussed such forms of the tubercle bacillus.

CONCLUSIONS

1. Acid-fast bacilli of the genus *Mycobacterium* were obtained from two patients with similar diseases.

2. Yeast-like bodies and phagocytized granules were found in skin biopsies from the patients.

3. Infected guinea pigs contained polymorphous phagocytized acid-fast material and globus-like bodies.

4. These unusual bodies appear to be associated with the microörganisms.

5. It is probable that the acid-fast microörganisms recovered are the aetiological agents of the disease in their respective hosts.

6. Neither microörganism fits the description of a previously recorded *Mycobacterium*.

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A LIPOID GROWTH FACTOR FOR THE TUBERCLE BACILLUS[1,2]

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Some bacilli are able to grow on certain simple media, while others need the presence of one or more accessory food factors. Haemolytic streptococci, pneumococci, diphtheria bacilli, meningococci and staphylococci are reputed to require the presence of traces of thiamin (vitamin B_1) (1). In addition to this the staphylococcus wants nicotinic amide (2) and, for anaerobic growth, uracil (3). The influenza bacillus needs the so called X-factor (haematin) and V-factor (coenzyme) (4). *Clostridium sporogenes, Welchii,* and *botulinum* require the "sporogenes factor" which is probably a fatty acid and is, among others, synthesized by the tubercle bacillus (5). Johne's bacillus when first isolated grows only in the presence of tubercle bacilli which contain an essential growth factor (6); the timothy bacillus has the same effect as the tubercle bacillus.

Tubercle bacilli are best isolated from sputum on potato or egg medium. Afterwards they can be grown on simple synthetic medium (Sauton, Long), but only if comparatively large amounts are planted (0.1 mg. or more). On egg media, growth occurs regularly after plantings of as little as 0.000,001 mg. or one hundred thousand times less (7). The same phenomenon has been observed in the growth of yeast which grows well in synthetic media after large plantings, but very poorly or not at all after small plantings. To obtain growth after small plantings the presence of bios is necessary; this has been shown to consist of a number of different growth factors, the principal being biotin (8), pantothenic acid (9) and meso-inositol (10). By analogy it seems probable that the failure of growth of the tubercle bacillus after small plantings on synthetic medium is due to the lack of one or more growth factors.

Theoretically it should be possible to control disease by eliminating the growth factors for the pathogenic microörganisms from the diet, where

[1] Presented at a session of the Pathological Section at the 34th annual meeting of the National Tuberculosis Association, Los Angeles, California, June 22, 1938.

[2] From the Laboratories of the Colorado Foundation for Research in Tuberculosis, Colorado College, Colorado Springs, Colorado.

this can be done without harm for the human organism. Even where the growth factor for the microörganism is also essential for man, as is the case for vitamin B_1, it is not impossible that a zone exists where still enough vitamin is present for human needs but not for the bacteria. It is, however, hardly possible to exhaust the vitamin reserves of the body in the short time taken by the acute infectious diseases. In chronic diseases, such as tuberculosis, conditions are ideal for control of the disease by diet. Recognition of the existence of a growth factor for the tubercle bacillus and its identification are necessary to put dietary management of the tuberculous on a scientific basis.

To demonstrate the presence of a growth factor, tubercle bacilli (H37) were grown on Corper's egg medium and on a synthetic medium of the following composition: asparagin 0.5, ammonium citrate 0.5, $Na_2HPO_4 \cdot 12\ H_2O$ 0.4, KC1 0.2, $MgSO_4 \cdot 7H_2O$ 0.1, ferric ammonium citrate 0.005, glycerol 8, agar 2, H_2O 100, brought to pH 7.0 with NH_3. The substances to be tested for the presence of a growth factor were dissolved in this medium or thoroughly emulsified if insoluble, the pH adjusted if necessary and the media sterilized at 15 pounds pressure. Slants of the medium were planted with 10^{-1} to 10^{-6} mg. tubercle bacilli and their growth compared with the growth on Corper's medium and on synthetic medium without any addition.

Egg yolk was rapidly dried at room temperature and then extracted with a mixture of equal parts of alcohol and ether. The alcohol-ether was evaporated under diminished pressure and enough of the residue added to synthetic medium to make the same lipoid concentration as in egg yolk (30 per cent). The extracted yolks consisted of a white powder, mostly protein, and enough of this powder was added to synthetic medium to make the same concentration as in egg yolk. Growth of tubercle bacilli appeared on Corper's medium up to plantings of 10^{-6} mg., on synthetic medium up to dilutions of 10^{-1} mg., on synthetic medium plus egg yolk proteins up to plantings of 10^{-1} mg. and in synthetic medium plus egg yolk lipoids up to plantings of 10^{-6} mg.

It is evident that the growth promoting qualities of the egg yolk pass entirely into the alcohol-ether extract, while the protein residue is without effect. The lipoid growth factor present in the alcohol-ether extract may be concentrated in the following manner. Twelve egg yolks are shaken with twice their weight of 95 per cent alcohol and an equal volume of petrol-ether. The alcohol and petrol-ether fractions are separated and the growth factor passes into the petrol-ether fraction. The petrol-

ether is evaporated and the residue extracted with 95 per cent alcohol; the growth factor goes into the alcohol. The alcohol is evaporated and the residue extracted with cold acetone in which the growth factor is insoluble. The yield is plus 6 gm. This extract is 100 times more active than the whole egg; 100 mg. added to 30 cc. of synthetic medium permits the bacilli to grow after plantings of 10^{-6} mg.

The unsaponified fraction remaining after saponification of this egg yolk extract with alcoholic potassium hydroxide shows no activity; the water soluble material is inactive and the fatty acids inhibit the growth of tubercle bacilli. It cannot be definitely stated that the growth factor is destroyed by saponification. The fatty acids and soaps (at pH 7.0) inhibit the growth of tubercle bacilli and might well mask the presence of a growth factor in this fraction.

TABLE 1

Effect of components of alcohol-soluble acetone-insoluble extract of egg yolk on growth of tubercle bacilli

MG. BACILLI PLANTED	10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}
Addition to Synthetic Medium:						
Alcohol soluble acetone insoluble extract	4	4	4	4	4	2
Unsaponifiable part	4	0	0	0	0	0
Fatty acids (soaps)	0	0	0	0	0	0
Glycerophosphate	4	3	0	0	0	0
Choline	3	1	0	0	0	0
Lecithin (Levene and Rolf)	4	4	0	0	0	0

4: numerous colonies; 3: 6 to 10 colonies; 2: 2 to 5 colonies; 1: 1 colony.

It was pointed out several years ago by one of us that lecithin favored the growth of tubercle bacilli and made growth possible throughout a liquid medium instead of on the surface only (11). A considerable part of the active fraction of the egg lipoids consists of lecithin. A sample of this lecithin showed no activity after purification according to Levene and Rolf (12). In this method the lecithin is precipitated with cadmium chloride and the cadmium later removed by alcoholic ammonia. Notwithstanding all precautions some of the lecithin may have been saponified during this process, thus masking any growth promoting qualities that the purified lecithin might have shown otherwise.

Coagulated egg white forms a fairly good culture medium, but extracts of egg white showed no growth promoting activity and sometimes inhibited the growth of tubercle bacilli. Extracts of potatoes were without effect, although potato medium is reputed to be equally effective in

the isolation of tubercle bacilli as egg medium. The growth factor may however be intracellular and difficult to extract for this reason.

Olive oil, linseed oil and beef tallow are without effect on the growth of tubercle bacilli, but lipoids from the liver and spleen of guinea pigs or rats permit growth after planting of 10^{-4} mg. The presence of the growth factor in the liver and spleen of the guinea pig may help to explain the

TABLE 2

Effect of various lipins and fats on growth of tubercle bacillus

MG. BACILLI PLANTED	10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}
Addition to Synthetic Medium:						
Linseed oil	1	0	0	0	0	0
Olive oil	4	0	0	0	0	0
Beef tallow	0	0	0	0	0	0
Tubercle bacillus phosphatide A3	3	1	0	0	0	0
Extract liver and spleen guinea pig,						
alcohol soluble	4	4	2	3	0	0
acetone soluble	4	0	0	0	0	0
Extract liver and spleen rat,						
alcohol soluble	4	4	4	4	0	0
acetone soluble	4	0	0	0	0	0

4: numerous colonies; 3: 6 to 10 colonies; 2: 2 to 5 colonies; 1: 1 colony.

TABLE 3

Effect of growth factors for other bacilli on the tubercle bacillus

MG. BACILLI PLANTED	10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}
Addition to Synthetic Medium:						
Vitamin B1	3	0	0	0	0	0
Nicotinic acid	3	0	0	0	0	0
Riboflavin	4	0	0	0	0	0
Uracil	4	0	0	0	0	0
Water extract egg yolk	4	0	0	0	0	0
Inositol	3	0	0	0	0	0

4: numerous colonies; 3: 6 to 10 colonies; 2: 2 to 5 colonies; 1: 1 colony.

invasion of these organs by the tubercle bacilli, but it is somewhat disconcerting to find the same factor present in the organs of the rat who is so much more resistant to tuberculosis.

No growth factor could be demonstrated in filtered synthetic medium on which tubercle bacilli had grown for six weeks, and the tubercle bacillus phosphatide A3 was equally without effect.

Thiamin (vitamin B_1), nicotinic acid, uracil, meso-inositol, and indol-

3-acetic acid were without effect. In a watery extract from egg yolk, which contains biotin and pantothenic acid, no growth factor could be demonstrated. Equally without effect was riboflavin (vitamin B_2) which we had previously isolated from the tubercle bacillus as will be reported elsewhere; it was tried in many different combinations and concentrations but none caused enhanced growth of the tubercle bacillus.

SUMMARY

A growth factor for the tubercle bacillus was demonstrated in extracts from egg yolk and from the liver and spleen of guinea pigs and rats. This factor is soluble in alcohol and insoluble in cold acetone. The addition of 0.3 per cent of the extract from egg yolk to synthetic medium permitted growth of tubercle bacilli after plantings of 10^{-6} mg. against growth only after planting of 10^{-1} mg. or more on synthetic medium without the egg yolk extract.

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BASOPHILIC ERYTHROCYTES IN SILICOSIS[1]

THOMAS A. NEAL

In reviewing the literature on the pneumonoconioses, one frequently encounters the note that various occupational dusts, other than lead, may be the cause of an increase in the usual number of punctate stippled erythrocytes. In his study of cement workers, Lehmann (1) found that the blood of these workers presented a higher frequency of basophilic granules in red cells than was found in lead poisoning. From the observation of basophilic stippled cells in the blood of nearly all silicotics, Riddell (2) suggested that silica might have a toxic action, although the number of such cells was not determined for any unit of blood.

Should it prove to be true that ordinary industrial dusts, exclusive of lead, provoke such a physiological response, then various tests for lead absorption and lead poisoning, based upon the determination of the number of red cells containing basophilic granules, must be devalued. At the present time, in many industries, the basophilic aggregation test, as described by McCord and his associates in several publications (3, 4, 5, 6), has been made a routine practice. Whenever, as the result of such tests in the dusty trades, red cells containing basophilic granules, in percentages above the usual, are observed in the blood of healthy workmen, the presumption is that exposure to lead exists. Obviously, then, if cement, coke, lime, silica, titanium dioxide or any other nonlead dust may induce such an increase in basophilic aggregations, this test for lead absorption and lead poisoning merits little value.

In order to broaden our present knowledge of the extent to which dusts, other than lead, may increase, beyond the normal, the number of stippled cells or basophilic aggregations in the blood of exposed workers, appropriate blood tests have been carried out in various dusty trades and among patients afflicted with pneumonoconioses, chiefly silicosis.

Small groups of workmen, totalling some 200 persons, engaged in dusty operations, were examined either by the basophilic aggregation test or for the total number of punctate stippled cells or both. The dusts involved in the exposures included titanium dioxide, lithopone, calcium carbonate,

[1] From the Bureau of Industrial Hygiene, Department of Health, Detroit, Michigan.

carbon, organic and inorganic pigments, cellulose and nitrocellulose. In the absence of lead as a constituent of these dusts, at no time have basophilic aggregations exceeded normal ranges nor have punctate stippled cells been encountered except rarely, and then only in low and expectable numbers. The techniques employed in the making of these tests conformed to those described by Hyler and Bradley (6).

To extend this inquiry further, 21 patients suffering from silicosis in varying degrees or stages and complicated by tuberculosis were subjected to the basophilic aggregation test and to quantitative counts of punctate stippled cells. As controls, 20 patients with frank pulmonary tuberculosis were similarly examined. In the silicotic group, no individual exhibited a percentage of basophilic aggregations as high as two, which figure is generally regarded as the upper limit for healthy adults. Fifteen of the 21 presented no preformed stippled cells, and the remaining 6 only such numbers as fall within normal ranges. Among the 20 control patients, only one showed basophilic aggregations in excess of the usual percentage for healthy adults. Seventeen of this group presented no stippled cells, two trivial numbers, but one revealed thirteen hundred stippled cells per million erythrocytes. An investigation into this patient's recent employment indicated that duties in the testing and adjustment of adding machines may have provided some exposure to lead dust, but this point has not been fully proved. Evidence, therefore, appears to exist for the belief that the blood of silicotics does not, regularly at least, present unusual numbers of basophilic erythrocytes as demonstrated either by the basophilic aggregation test or stippled cell counts.

SUMMARY

From several series of examinations of the blood of workers in nonlead dusty trades, and of hospital patients suffering from tuberculosis or silicosis with tuberculosis, no evidence was found to indicate that common industrial dusts, other than lead or its compounds, provoke an increase in the usual number of red cells containing basophilic granules.

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IMMUNIZATION AGAINST TUBERCULOSIS[1]

A Study of the Essential Factors

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Since 1882 when Koch first announced the discovery of the tubercle bacillus numerous attempts have been made to combat or prevent the spread of the disease in various communities.

Among these efforts there have been many attempts at vaccination against tuberculosis, the best known being those with tuberculin, dead tubercle bacillus, and more recently with BCG.

In animal experiments the study of the effect of prophylactic inoculations or vaccinations against tuberculosis can be carried on, as a rule, with a fair degree of accuracy. However, in studies with human beings the very nature of the problem makes the selection of controls most difficult, because of the many variable factors which may influence the inception and the clinical course of tuberculosis.

If an experiment of this type based on a study of children were to be ideally controlled the following factors would have to be considered:

Environmental Conditions

1. Intelligence and coöperation of parents
2. Difference in localities
3. Time differences

Exposure Conditions

1. Frequency of exposure
2. Amount of sputum expectorated
3. Number of microörganisms in sputum
4. Intensity of exposure

Other Factors

1. Age at first exposure
2. Racial differences
3. Reliable diagnosis at death
4. Following controls and vaccinated cases in a similar manner
5. Keeping contact with all cases
6. If vaccinated cases are to be separated for a period of time, controls should be separated for a similar period
7. Study of adequate number of controls and vaccinated cases to minimize a result due to chance distribution

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[1] From the Bureau of Laboratories, Department of Health, New York City.

In no study thus far reported have all these factors been specifically mentioned.

In some studies the mortality rate from tuberculosis of the general population was compared with that of the vaccinated or studied group; in others a different age group served as a control; in some the tuberculosis mortality of vaccinated children was compared with that of previous years; in still others, the control group was less carefully followed than the vaccinated one. In brief, then, the conclusions derived from such studies cannot be considered as final.

During the past eleven years a study on the efficacy of BCG vaccination against tuberculosis in children has been carried on in New York City by the Bureau of Laboratories of the Department of Health. Up to April 1, 1937, 1,830 children of tuberculous families have been followed, of which 880 were vaccinated and 950 served as controls.

In the course of these eleven years of study, the importance of selecting adequate controls has been emphasized repeatedly. In certain instances the omission of a single factor would greatly alter the conclusions.

It is the purpose of this paper to point out the value of controlling cases as accurately as possible, using as examples the children followed in the BCG study in New York City.

SELECTION OF CONTROLS

At the outset of the study an attempt was made to control the experiment by dividing the children into two equal groups, those vaccinated and those not vaccinated. Under this system a physician was assigned a number of cases and was told to vaccinate half of the group. These children were referred from homes where a known case of tuberculosis existed, and were accepted for study when still under one year of age. The attempt was made to follow both the vaccinated and the control cases with equal care. They were visited every month by nurses, and every three to six months by the pediatricians. Tuberculin tests were made and X-rays taken at fairly regular intervals in both groups.

It is evident that by this method of selection the tendency might be to inoculate the children of the more intelligent and coöperative parents, and to keep the children of the noncoöperative parents as controls. This would be a serious error, since the coöperative parent would not only observe more careful precautions, but would usually bring the child more regularly to the clinic for instruction as to child care and feeding.

The procedure just outlined was followed from 1926 to January 1,

1933, and in all 955 children were studied, 435 of whom were vaccinated.

Realizing that these difficulties existed the procedure of selection was changed on January 1, 1933 so that alternate children were routinely vaccinated, the remainder serving as controls. The selection was made at the office, as soon as the names were received, and before they were assigned to the pediatricians. If a case refused vaccination, but was otherwise fully coöperative, it was listed as "routine BCG vaccination—refused vaccination" and used as a control. This would be matched by a case selected originally as a control, but who requested vaccination. If a family was wholly uncoöperative it was not taken up for study. In

TABLE 1

Results of BCG vaccination before alternate selection of control and vaccinated cases

RESULTS 12/15/26 TO 1/1/33	NUMBER	TUBERCULOSIS DEATHS	TUBERCULOSIS MORTALITY
			per cent
BCG vaccinated cases	439	3	0.7
Controls	527	16	3.0

Results of BCG vaccination after alternate selection of control and vaccinated cases

RESULTS 1/1/33 TO 9/1/36	NUMBER	TUBERCULOSIS DEATHS	TUBERCULOSIS MORTALITY
			per cent
BCG vaccinated cases	383	6	1.6
Controls	361	4	1.1

all, 744 children were observed from January 1, 1933 to September 1, 1936, 383 being vaccinated and 361 held as controls.

The results obtained in the two periods of observation are shown in table 1.

In the first period the tuberculosis mortality of the controls was over four times that of the vaccinated cases. In the second period there were no significant differences.

It would seem, therefore, that the manner of selecting cases for vaccination or as controls exerted a marked influence on the final results obtained.

However, an attempt to explain the differences in the two periods first demands consideration of the following possibilities:

1: Was there any change in proportional exposure to positive sputum?
2: What was the racial grouping in the respective periods?

3: What was the proportion of lost cases in the two series?
4: What effect had the number of autopsies on the results of the two series?
5: Could these differences be the result of chance distribution?

A complete study of these factors will be found in a forthcoming article. Suffice it to say, they did not appear as sufficiently strong agents to influence the results to the degree already shown.

EXPOSURE CONDITIONS

Probably the most important single factor in a study of tuberculosis prevention is a knowledge of the exposure conditions. The frequency of exposure, the amount of sputum expectorated, the number of bacilli in the sputum, and the intensity of exposure should be known in every instance for a proper summation of the individual case.

It is conceivable that one child may be massively exposed to a parent who comes home from the sanatorium one week in every month, whereas

TABLE 2

Exposure conditions of total cases studied

TOTAL CASES FOLLOWED	EXPOSED TO POSITIVE SPUTUM			EXPOSED TO NEGATIVE SPUTUM			NO KNOWN EXPOSURE		
	Cases	Tuberculosis deaths	Mortality	Cases	Tuberculosis deaths	Mortality	Cases	Tuberculosis deaths	Mortality
			per cent			*per cent*			*per cent*
2,454	1,126	34	3.0	956	2	0.21	372	3	0.9

another child may be very little exposed to a parent with positive sputum, living at home but maintaining careful precautions.

One patient may cough up a great deal of sputum containing practically no bacilli whereas another may cough up a small amount of sputum loaded with tubercle bacilli.

It has been our custom in New York City to record the exposure conditions on every case, and to concentrate all sputa in which microörganisms are not found routinely.

Just how important a knowledge of exposure conditions is, may be seen from table 2.

RACIAL DIFFERENCES

The high mortality from tuberculosis among the Negroes has been well recognized. However, in spite of this, certain studies have been made without consideration of the racial aspect.

A clear example of the importance of this factor can be obtained by an examination of the cases followed in the BCG study after January 1, 1933 (table 3).

Whereas the Negro and Porto Rican children contributed only 35 per cent of the total cases followed, they totalled 90 per cent of the tuberculosis mortality.

It is obvious, therefore, that the racial influence in any study of tuberculosis immunization is important and should be taken into consideration.

LOST CASES

In a city, such as New York, where active measures are being taken to isolate those with tuberculosis, to teach proper precautions, and to aid in the general care of the families, the mortality rate from tuberculosis in families, after the contact is known, is rather small as compared with the tuberculosis mortality in families where the focus was not previously

TABLE 3

Effect of racial factor on tuberculosis mortality of total cases followed after January 1, 1933

TOTAL CASES ALL RACES	TOTAL TUBERCULOSIS DEATHS	NEGRO AND PORTO RICAN				WHITE			
		Cases	Per cent of total cases	Tuberculosis deaths	Per cent of tuberculosis deaths	Cases	Per cent of total cases	Tuberculosis deaths	Per cent of tuberculosis deaths
744	10	262	35.2	9	3.4	482	64.8	1	0.2

discovered. It is of the greatest importance, therefore, that contact be kept with all followed cases.

Every attempt has been made to keep in touch with the families studied. The nurses visit the homes every month, asking each time whether the parents or guardians have any intention of moving; the name of a close friend or relative is obtained to whom they could go for information if the family disappears; it is recorded if the father is a World War veteran, for he will keep contact with the Veterans Bureau to obtain his pension; if the family has life insurance it is noted as well as the number of the policy; if other children in the family are attending public school the number of the school is obtained as well as the names of the children; and in certain cases it is recorded whether the family subscribes to gas and electricity, for the poorer homes have to place a deposit with the companies and usually transfer the deposit to their new address.

In spite of all these efforts, families do disappear and all attempts to trace many of them are unavailing (table 4).

The necessity for following all cases closely is emphasized when one considers that the mortality rate of these cases was only[2]

	Tuberculosis Deaths	*Tuberculosis Mortality*
Vaccinated, 383	6	1.6%
Controls, 361	4	1.1%

NECESSITY FOR RELIABLE DIAGNOSIS AT DEATH (AUTOPSIES)

It became evident early in the study of BCG immunization that autopsies were necessary on all cases that died. This was important for several reasons.

First, autopsies in both groups were of great importance in order to ascertain definitely the cause of death. Furthermore, it was necessary

TABLE 4

Number of cases lost since January 1, 1933

	CASES FOLLOWED	NUMBER LOST CASES	PER CENT LOST CASES	LESS THAN 1 YEAR	1 YEAR	2 YEARS	3 YEARS	4 YEARS
Vaccinated	383	11	3.1	4	5	1	1	0
Control	361	31	8.7	6	17	7	1	0

to determine, in the case of vaccinated children, the microörganism causing death, in order to ascertain whether it was due to the bovine bacilli of BCG or to a human strain.

Since an increased number of autopsies in either group might cause the apparent tuberculosis mortality to change, it is obvious that the autopsy record must be examined (tables 5 and 6).

It would seem from these figures that the increased number of autopsies among the vaccinated cases had a definite influence upon the actual tuberculosis mortality of the group observed after January 1, 1933.

One is struck immediately with the absolute necessity for an autopsy examination on every case followed in a study of this type. If a case dies of pneumonia, gastrointestinal intoxication, malnutrition, convulsions, *status lymphaticus*, etc., with or without a positive tuberculin test, with or without a positive X-ray picture, even without any known ex-

[2] In our study the tuberculosis mortality rate from January 1, 1933 to January 1, 1938 was 1.19 per cent in 506 BCG treated cases and 1.27 per cent in 474 control cases.

posure, it must be considered as a questionable case unless an autopsy is performed.

In our series, two children have died of tuberculosis without any known exposure, and four with negative tuberculin tests.

Under these circumstances it becomes evident that in any series of cases, including our own, the results as to tuberculosis mortality must be considered inaccurate without 100 per cent postmortem examinations.

TABLE 5

Postmortem examinations before and after January 1, 1933

BEFORE 1/1/33	TOTAL CASES	TOTAL DEATHS	AUTOPSIES	
			Number	Per cent
Vaccinated	437	34	16	47.0
Controls	527	42	16	38.1
After 1/1/33				
Vaccinated	383	15	12	80.0
Controls	361	20	13	65.0

TABLE 6

Accuracy of clinical diagnosis as determined by postmortem examinations

BEFORE 1/1/33	CASES AUTOPSIED	CASES DIAGNOSED AS TUBERCULOSIS BEFORE AUTOPSY	CASES DIAGNOSED AS TUBERCULOSIS AFTER AUTOPSY	DIAGNOSIS CHANGED AFTER AUTOPSY TO DIAGNOSIS OF TUBERCULOSIS
Vaccinated	16	2	2	0
Controls	16	6	8	2
AFTER 1/1/33				
Vaccinated	12	2	6	4
Controls	13	1	2	1

This is especially true when the mortality rate is low and when several deaths on either side may change the results considerably.

It is interesting to study the cases whose diagnosis of death was changed following autopsy examination (table 7).

Of the children diagnosed at death as nontuberculous and not autopsied the following are certainly to be questioned:

4 cases of bronchopneumonia with positive tuberculin tests
5 cases of bronchopneumonia, never tuberculin tested

1 case of lobar pneumonia with positive tuberculin test
1 case of convulsions with positive tuberculin test
1 case of acute capillary bronchitis, never tuberculin tested
1 case of *status lymphaticus* with positive tuberculin test
1 case of gastrointestinal intoxication with positive tuberculin test

The above diagnoses were made by the attending staff of the hospitals in which the children died.

TABLE 7

Babies diagnosed at death as nontuberculous, but proved on autopsy to have died of tuberculosis

NAME	PRE-AUTOPSY DIAGNOSIS	POST-AUTOPSY DIAGNOSIS	MANTOUX	X-RAY
		Control Cases (before 1/1/33)		
P. E.	Gastrointestinal intoxication	Miliary tuberculosis	Negative	Positive
M. M.	Metastasis from teratoma	Miliary tuberculosis	Positive	Positive, diagnosed as neoplastic
		Vaccinated Cases (all after 1/1/33)		
P. F.	Cerebral irritation, sudden death	Miliary tuberculosis	Positive	Positive
J. K.	Gastrointestinal intoxication and bronchopneumonia	Tuberculous pneumonia and slight miliary tuberculosis	Negative	±
R. M.	Bronchopneumonia	Tuberculosis	Positive	None
J. W.	Bronchopneumonia	Miliary tuberculosis	None	None
		Control Cases (after 1/1/33)		
H. M.	Pneumonia	Pulmonary tuberculosis, tuberculous meningitis	None	? Pneumonia

It is also possible that certain of our dead cases, lacking autopsy, who were diagnosed as tuberculosis and placed in that mortality group, were nontuberculous.

The mere fact that eight vaccinated children have already died of tuberculosis, does not by itself indicate a lack of efficacy on the part of the BCG vaccine.

It is necessary, before any answer to our problem is obtained, that every case dying of tuberculosis be carefully studied, necessitating an autopsy, a bacteriological examination of the tissues, and an accurate knowledge of the exposure.

TABLE 8

Vaccinated cases who died of tuberculosis

PARENTERALLY VACCINATED	EXPOSURE	SPUTUM OF TUBERCULOSIS CASE	AGE AT VACCINATION	AGE AT DEATH	AUTOPSY	BACTERIOLOGY
				months		
R. D.	Birth to 3 months	Positive	3½ months	8	Tuberculosis	Human tubercle bacilli
J. W.	Birth to death	Positive	3 weeks	4½	Tuberculosis	Human tubercle bacilli
P. F.*	Birth to 5¼ months	Positive	1½ months	9¾	Tuberculosis	No bacteriology. Tissues placed in formaldehyde
J. K.	Birth to 1½ months	Positive	1½ months	3	Tuberculosis	Human tubercle bacilli
R. M.	Father with positive sputum, birth to 1 month. Mother with negative sputum, birth to death	Positive	1¾ months	13	Tuberculosis	Human tubercle bacilli
J. P.	Birth to 9 months	Positive	9½ months	14¾	Tuberculosis	Human tubercle bacilli
ORALLY VACCINATED						
N. M.†	None known	Positive	1st week	3	0	None
M. R.‡	Occasional exposure. Birth to death	Positive	1st week	32	Tuberculosis	Human tubercle bacilli
L. L.	Birth to death	Positive	1st week	8	Tuberculosis	Human tubercle bacilli

* This case was autopsied and all specimens saved were placed in fixing solution. This prevented any bacteriological studies.

† This baby was born of a mother dying of an overwhelming tuberculous infection. The latter died shortly after giving birth. The child was vaccinated by mouth during the first week, and died of tuberculosis at 3 months of age. No autopsy was performed. Diagnosis made on X-ray findings. Possibly a placental transmission.

‡ This baby died of bronchopneumonia following pertussis. X-ray appeared suggestive of miliary tuberculosis. However, no tubercles were found in the lungs on autopsy, macroscopically or microscopically. Bacteriological examination was negative for tuberculosis in the lung tissue but positive in mediastinal lymph nodes. No evidence of tuberculosis in other parts of body.

This is of particular importance in the case of vaccinated children, since, as has been stated before, it is conceivable that one might attribute the deaths to BCG unless bacteriological examinations proved otherwise. Thus far no authentic cases have been reported in the literature.

A study of the nine vaccinated cases dying of tuberculosis is of great interest (table 8).

From table 8 several facts can be obtained: (*1*) All cases except one (N. M.) were definitely exposed to virulent human tubercle bacilli in their homes before vaccination. (*2*) All cases except N. M. were autopsied. (*3*) Of the 8 cases autopsied, 7 were found to have human tubercle bacilli in their tissues, and in one case bacteriological examination was impossible due to the tissues being placed by mistake in fixation solution.

The question naturally arises as to whether these deaths were due to a tuberculous infection previous to vaccination, or whether the vaccination was an inadequate protection against a subsequent infection. This is difficult to answer.

SEPARATION OF CONTROLS AND VACCINATED CASES

The previous question brings up the problem as to what results would be obtained if cases were separated before vaccination to prevent the inoculation of a child in the preallergic phase, and if the same cases were separated for a sufficiently long period after inoculation to permit the vaccine to take effect.

For a more accurate answer it would be necessary to separate all subjects for a minimum of three months before and three months after vaccination.

We have found it a dangerous policy to institutionalize children during the first three months of life, since they so often contract infections in the hospital or home to which they are sent. As a matter of fact it appears that many more babies, so separated, died during this period of nontuberculous causes, than would have died of tuberculosis had they remained at home.

Table 9 brings out clearly the danger of institutionalizing babies at such an early age.

However, in the course of our studies a certain number of children chanced to be separated for three months before and three months after vaccination. It is to this group then that we must look for any trend that might give an indication of the value of the inoculation.

One may for this study take all such cases followed since the onset of the BCG experiment in New York City, for all were segregated from tuberculous infection during the six months period (table 10).

TABLE 9

Study of the nontuberculous mortality of well infants (including controls and BCG vaccinated cases) hospitalized during the first three months of life (mortality during first 3 months of hospitalization)

INFANTS HOSPITALIZED DURING FIRST THREE MONTHS OF LIFE AS WELL BABIES		INFANTS NOT HOSPITALIZED DURING FIRST THREE MONTHS OF LIFE	
Total number	120	Total number	949
Number of nontuberculous deaths in first three months	14	Number of nontuberculous deaths in first three months	9
Percentage	11.6	Percentage	0.9
Cause of deaths:		Cause of deaths:	
Gastrointestinal intoxication	10	Gastrointestinal intoxication	5
Pneumonia	2	Pneumonia	4
Foreign body in trachea	1		
Thymus (?)	1		

Note: Prematures who died under one month of age are not included in the above figures.

TABLE 10

Cases separated three months before and three months after vaccination

	NUMBER OF CASES	TUBERCULOSIS DEATHS	TUBERCULOSIS MORTALITY	NUMBER NEVER EXPOSED
Vaccinated	233	1	0.43%	142 (61%)
Controls	195	3	1.50%	99 (51%)

Eliminating those cases never exposed

	NUMBER OF CASES	TUBERCULOSIS DEATHS	TUBERCULOSIS MORTALITY
Vaccinated	91	1*	1.1%
Controls	96	3†	3.1%

* This child was born of a mother dying of tuberculosis; was never exposed; died at 3 months.

† One case with no known exposure died of tuberculosis at 15 months.

SUMMARY

1. In the studies of immunization of human beings against tuberculosis the proper selection of controls is most difficult.

2. The most important factors to be considered in the study of human immunization against tuberculosis are outlined.

3. The method of alternate selection of controls and vaccinated cases appears to be essential.

4. The effect of different exposure conditions, racial factors, the necessity of keeping contact with all cases, and the necessity for a reliable diagnosis at death are also stressed.

5. This paper is concerned only with a study of methods used, and no attempt is made to judge the efficacy of BCG in immunization against tuberculosis. The latter will be the subject of a future communication, since at the present moment we feel that our available data are insufficient for final judgment.

TUBERCULOSIS IN BRITISH GUIANA[1]

OLIVER M. FRANCIS[2]

British Guiana lies on the north-eastern coast of South America between parallels 1° and 8° north latitude and meridian 57° and 61° west longtitude. Its area is 89,480 square miles. In 1936 the rainfall was 104.09 inches; the average mean shade temperature 80.7°F.; the mean vapor pressure 0.860 inch equal to 29.1 millibars; and the estimated population 332,898 distributed mainly along a narrow strip of coast line, 270 miles long, and for limited distances up rivers and creeks and within short distances from their banks.

EXTENT OF TUBERCULOSIS

In 1936 there were 313 notifications and 261 deaths from tuberculosis of all forms in the colony. The death rate from this disease was 0.78 per 1,000 of the population. The figures for the neighboring South and Central American countries have not been available. The figures for the British West Indian colonies are similar. The British Guiana figure places the colony among countries with low tuberculosis death rates.

History of incidence: There has been a steady decline in tuberculosis incidence and mortality in the colony during the past fifty years. According to Godfrey (1) tuberculosis obtained a foothold in the colony during the period 1840 to 1873. At the commencement of this period the incidence was described somewhat erroneously as zero, and at the end of the period the death rate was given as 2.40 per 1,000. By 1843 the death rate had risen to 3.19 per 1,000. Thereafter there has occurred a fairly steady fall to the present figure of 0.78 per 1,000.

The secular trend of tuberculosis mortality in the colony shows that there was a steep decline in mortality from this disease during the decade of 1917 to 1926, there being an average decrease in the death rate of 2.8 per cent per annum as compared with 1.1 per cent during the decade 1927 to 1936.

[1] From a paper read at a meeting of the British Guiana Branch of the British Medical Association, Georgetown, British Guiana, June 18, 1937.

[2] King Edward VII Memorial (Tuberculosis) Dispensary, Georgetown, British Guiana.

Tuberculosis ranks seventh as a cause of death in the colony, being lower in this respect than malaria, nephritis (including uraemia), bronchitis, diseases of the heart, pneumonia and enteritis.

RACIAL INCIDENCE

Morbidity: The average annual incidence of the disease in each race in the colony, as derived from the total notifications during the period 1927 to 1936 is as follows: Europeans 0.56, East Indians 0.85, the mixed races 1.11, the Aboriginal Indians 1.20, the black race 1.31, the Portuguese 1.33, and the Chinese 1.45 per 1,000 of their respective race groups. General deductions from these rates should be drawn with reserve especially as the number of notifications among, as well as the total population of, the European, Aboriginal Indians, Chinese and Portuguese are small as compared with those of the black and East Indian races. A detailed study has been made of the incidence in the black and East Indian races which together constitute over 81 per cent of the population of the colony and also furnished over 81 per cent of the total notifications during the period 1927 to 1936. The rates when examined statistically showed:

1: That the total rate of the black race was significantly higher than that of the East Indian race.
2: The rate in either sex of the former race was significantly higher than that of either sex of the latter race.
3: In both races the rate in the males was significantly higher than that in the females, in the East Indian race this being remarkably so.
4: In both sexes of both races the bulk of the notifications occurred in the age groups between 15 and 50 years and the peak occurred earlier in females than in males.

Racial differences in tuberculosis mortality, disease and infection are commonly observed. Whether these differences are due to race *per se* or to the difference in the social and hygienic conditions under which the races live, entailing thereby a difference in the degree of their exposure to infection, is still a moot question. The following figures give the mortality from pulmonary tuberculosis of some of the race groups in New York City during the period 1919 to 1921: Chinese 8.25; Negroes 3.98; Irish 3.00; Scotch 1.81; English 1.36; Jews 0.86 per 1,000.

In the United States of America where large numbers of the black race live side by side with the white race the tuberculosis mortality in

the former is about three to four times that in the latter, while that in the Indian Aborigines is about three times that in the black race. Pinner and Kasper (2) have shown that the pathology, the clinical manifestation and the shortened duration of the disease in the black race, all point to lower resistance in that race as compared with the white race. Opie (3) found in Philadelphia no significant difference in the percentages of tuberculin positive reactions in white and colored school children, but Aronson (4) found significantly lower percentages in white school children than in colored ones living under similar rural conditions in the southern states. The evidence is abundant, irrespective of the cause, that tuberculous infection, morbidity and mortality are higher in the black race than in the white race living in the same areas.

With respect to the East Indian race, tuberculosis is very prevalent in this race in India. Rogers (5) analyzed 5,000 postmortem examinations made at the Medical College Hospital, Calcutta, and showed that pulmonary tuberculosis caused 17 per cent of the mortality in the medical wards of the hospital while 8 per cent showed tubercle in addition to other causes of death, or a total of 25 per cent with gross lesions of tuberculosis. Lankester (6) in 1920 gave tuberculosis rates in the native population in India varying between 12.8 to 3.3 per 1,000. Sprawson (7) in 1937 estimated that there were two million cases of tuberculosis in India. In the cities of Poona and Ahmenhabad, one out of every twelve deaths and, in Cawnpore, one out of every eleven was due to tuberculosis. The tuberculosis death rate at Calcutta was 2.4 per 1,000 in 1934 and was increasing.

The black and East Indian races living side by side in the colony seem therefore to be equally susceptible to the disease. The higher incidence in the black race is therefore a matter of interest. The remarkably low incidence in the East Indian female is particularly so. The following probably furnish satisfactory explanation of these differences:

1: A very large proportion of the black race live in towns the overcrowded areas of which have a preponderance of this race; 33.4 per cent of the black population live in towns constituting 53.7 per cent of the population of these towns.

2: The greater proportion of East Indians living in towns are the well to do who are not exposed to overcrowding.

3: A very large proportion of East Indians live on plantations where overcrowding is less than in towns; 44.7 per cent of the East Indian population live on plantations constituting nearly 80 per cent of the population of plantations.

4: It is a matter of common knowledge and observation that the East Indian woman as compared with the black woman or the East Indian man is conspicuously absent from the crowds and from crowded places of all kinds in the colony. She is therefore likely to escape the dangers of infection which lurk in these places.

5: The incidence of tuberculosis is significantly higher in towns than in villages and significantly higher in the latter than on plantations. The incidence is significantly higher in the black race in towns and significantly higher in the East Indian race on plantations where the race with the higher incidence is overwhelmingly more numerous. In villages where the numbers of these races are about equal and conditions are identical the difference in the incidence is not significant.

These facts suggest that the difference in the incidence in the two races locally is environmental rather than racial.

CAUSAL FACTORS AND TYPE OF DISEASE

The type of disease which occurs in the colony is mainly pulmonary. During the ten year period 1927 to 1936 over 96 per cent of the patients treated for tuberculosis in the public hospitals of the colony suffered from pulmonary or laryngeal tuberculosis, while less than 4 per cent suffered from other forms of the disease. The reports of the Government Veterinary Surgeon show that the incidence of tuberculosis in cattle is very low (less than 1.5 per cent in all areas). Milk is boiled before use, and probably more than half the milk ingested is thus treated more than once. Tuberculous organs from the pig are encountered in meat inspection. However pork is so thoroughly cooked before ingestion in this colony that the risks from this source are about just as small as those from beef or milk.

Housing and nutrition: Official reports show that considerable overcrowding exists among the poorer classes in towns and that the type of houses occupied by these classes needs much improvement. The reports of the Health Visitors of the British Guiana Tuberculosis Society show that much overcrowding exists in rooms from which cases have been notified and that the opportunity for contact infection has been abundant. Fifteen per cent of the cases investigated by the Visitors in 1936 were contacts; the proportion would probably be larger if all cases could be investigated. Jessel (8), Wood (9), and Schuman (10) have shown that the case with positive sputum is the chief single factor in the spread of pulmonary tuberculosis, and conversely, that efficient isolation

of the case with positive sputum is the greatest single factor in the control of the disease.

No survey on nutrition has yet been conducted and no figures are available to indicate the nutritional condition of the community generally or of any large group of the population. However, local medical practitioners urge that the state of nutrition of a large section of the population is definitely low. The association of tuberculosis and malnutrition is well recognized. Wolff (11) has remarked that "the general course of tuberculosis epidemiology in the next years will depend in the first place, as our experience in the world war demonstrates, upon the nutrition of the bulk of the people;" and Cathcart (12) that "tuberculosis is the one disease to which there seems to be fairly good evidence that a well fed body is more resistant."

CONTROL AND TREATMENT

Tuberculosis was made compulsorily notifiable in January, 1912. In the meantime there was established in 1907 the British Guiana Society for the Prevention and Treatment of Tuberculosis. This society receives financial support from the government of the colony, the municipality of Georgetown, and from the general public. The first dispensary was established in 1908. There are now six dispensaries at which fifteen practitioners serve as honorary physicians. The society employs five health visitors, two out-patient nurses and one dispenser. Patients attend the dispensaries from all parts of the colony. The sphere of operation of the health visitors however is confined to the towns and the villages and settlements along the main roads within a radius of about twenty-five miles from Georgetown. They do not visit sugar plantations or river settlements. They investigate the condition of patients and their homes, their reports being referred to the Medical Officer of Health of the area. Contacts are requested to attend a dispensary for examination and subsequently for screening at the Public Hospital.

The two principal Public Hospitals of the colony have special tuberculosis wards. In addition there exists just across the river from Georgetown the Best Tuberculosis Hospital with accommodations for 36 patients. This hospital was established in 1922. Operations are now in progress for the establishment on the same site of a fully equipped Sanatorium Hospital with accommodation for 90 patients in all stages of the disease. Artificial pneumothorax treatment, phrenic evulsion and other forms of collapse therapy are practised in some hospitals.

Legislation for the control of tuberculosis follows the lines of English legislation. Notification is compulsory. Hospitalization may be ordered by a Justice of the Peace on the certificate of a medical practitioner that a person is suffering from the disease and is lodged under conditions wherein he cannot be effectively isolated so as to prevent the spread of the disease. Tuberculosis being included as an infectious disease in the law, all the restrictions placed on sufferers from infectious disease apply to sufferers from this disease, such as, the prohibition to use public conveyances, to be engaged in the milk trade, etc. The by-laws regulating the sale of milk ensure that all cow-byres and pens are inspected and registered, and that all those engaged in the milk trade are free from tuberculosis or other infectious disease.

I am thankful to the Surgeon General for his permission to publish this paper, to Mr. H. D. Huggins, M.Sc. (Cornell) for kindly checking the statistical part, and to the clerical staff of the Government Public Health Department for their assistance in collecting the figures.

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CHRONIC NONTUBERCULOUS INFECTIONS OF THE LUNG[1,2]

A Clinical Discussion

ROBERT G. BLOCH AND BYRON F. FRANCIS

Among the chronic, nontuberculous, pulmonary infections, bronchiectasis and abscess are of the greatest importance. They are the only nonspecific pulmonary infections which, numerically and aetiologically, to some extent present a public health problem, especially bronchiectasis. They are, therefore, given the chief place in this paper.

A discussion limited to the clinical factors of these conditions without consideration of roentgenological diagnosis did not seem a fruitful task at first, especially since a complete review of all clinical aspects was not intended. The present-day chest specialist does not want to, and cannot, dissociate the clinical and roentgenological aspects of his field. Nevertheless, the study of only the clinical material which has accumulated over a period of time results in a number of striking observations, aetiological and clinical. Together with other values they have so much bearing on the diagnosis that the importance of roentgenological examination seems to dwindle somewhat if we think of recognizing these particular lung involvements as such rather than diagnosing their exact distribution and extent. This is especially true of bronchiectasis. There are few diseases where the anamnesis together with physical examination leads so securely to a diagnosis.

In a moderately sized general hospital and clinic, a call for all patients' records with the diagnosis "bronchiectasis" brings out a considerable number of cases; in our institution there were somewhat over 200 in a ten-year period. In many of these, bronchiectasis was diagnosed as a minor condition of little significance. In others, it was merely registered as an impression without much demonstration of facts. This is quite justified. The most essential, although secondary, aetiological

[1] Read as part of the Symposium on *Chronic Nontuberculous Infections of the Lung* at the joint session of the Pathological and Clinical Sections at the 34th annual meeting of the National Tuberculosis Association, Los Angeles, California, June 21, 1938.

[2] From the Department of Medicine, University of Chicago, Chicago, Illinois.

factor of the condition is chronic cough resulting from some disturbance of the bronchial function and from the entrance of infected material into the bronchi. It is reasonable to assume that, in a majority of individuals with cough of long duration and chronic drainage from the upper respiratory tract, a bronchiectasis of at least minor degree may have developed. In middle-aged and elderly individuals we do not look upon this as a condition warranting iodized-oil injections and extensive therapy. Not even in the presence of suggestive physical findings in the lungs, we believe, should one exert such patients by diagnostic and therapeutic manipulations if their symptoms do not exceed those of a moderate, chronic bronchitis. Patients of this category were not tabulated in the series which is to follow. For the same reasons the series does not include those in whom bronchiectasis was a development secondary to adult tuberculosis. Here also the condition is usually of minor degree or strangely lacking its outstanding symptoms. This group is mentioned separately because it offers the opportunity of discussing an important point in the differentiation of active tuberculosis and a bronchiectasis resulting from it. It is still a widespread belief that the activity of pulmonary tuberculosis can be judged by the presence or increase of râles, its inactivity by their absence or disappearance. Patients with persistent râles are apt to be treated for active tuberculosis long after their lesions are well healed. Some degree of bronchiectasis may be expected in the lung of any patient in whom, besides the mechanical effect of cough and the invasion of the bronchial linings by a mixed infection, the traction from increasing fibrosis has played havoc with the walls of at least the finer bronchial elements. After a long period of observation with persistently negative sputum, râles, apical or elsewhere, may indicate nothing more than a residual bronchiectasis or bronchiolectasis, even when there is roentgenological evidence of cavitation.

The series of cases selected for presentation has been confined to sixty patients in whom moderate or pronounced symptoms of bronchiectasis were the sole reason for their having sought medical aid, in whom the presence of the condition was ascertained beyond doubt, and in whom a reasonable effort had been made to find extrapulmonary aetiology. Almost all of these individuals had an advanced degree of bronchial dilatation.

The tables which follow attempt to demonstrate some important clinical and therapeutic points.

Most of the patients were of the young adult age. Only four were

younger than 15, the youngest, 10 years old. Twelve patients were above 40, the oldest, 67 years. The average age of 14.2 years at the beginning of symptoms was estimated in the following way: in 25 per cent of the patients who gave no definite or approximate time of the onset except the characteristic information of having "coughed all their life," "ever since they can remember," "since childhood," the onset was assumed at the age of 10; "since infancy" was interpreted to mean the

TABLE 1

Bronchiectasis

University of Chicago Clinics

60 patients	28 male 32 female
Average age	28.8 years
Average age at onset of symptoms	14.2 years
Average duration of chronic symptoms	14.6 years

TABLE 2

Bronchiectasis

Aetiology

Primary condition preceding onset of chronic symptoms (patients' information):	
Measles	4
Scarlet fever	2
Whooping cough	6
Pneumonia	7
Tuberculosis (in infancy)	2
Sinusitis	3
Asthma	1
Cold	5
Foreign body	2
Influenza	1
None given	27
	60

age of 5, and "for many years" to date back twenty years in patients of middle age or more. By comparison of the averages of age and duration of symptoms, it becomes clear that, in the overwhelming number of patients, bronchiectasis begins early in life.

In the aetiology we differentiate between the primary or predisposing conditions, which consist largely of the array of infectious diseases involving the upper respiratory tract, and the secondary or immediate cause of the chronic bronchial symptoms. Among these secondary

causes, involvement of the nasal sinuses, chiefly the maxillary ones, is increasingly recognized as playing the dominant rôle in the origin of bronchiectasis. In our series the findings of 45 per cent with definite sinus involvement hardly represent the actual frequency of this aetiology. The inclusion of the 33 per cent with indefinite sinusitis, bringing the figure to a total of 78 per cent, probably comes nearer to the truth. The discovery of a sinus condition is not only of aetiological interest but of great therapeutic importance. It is necessary, therefore, to exhaust all

TABLE 3

Bronchiectasis

Aetiology

Secondary cause of chronic symptoms (from findings)

Definite sinusitis		27 (45%)
Maxillary	15	
Multiple (maxillary and other sinuses)	6	
Pansinusitis	6	
Indefinite sinusitis		20 (33%)
Other chronic upper respiratory infections		7 (12%)
Rhinitis	5	
Tonsillitis	1	
Nasal polyp	1	
Bronchitis (without upper respiratory involvement)		3 (5%)
Infectious	1	
Allergic	1	
Dust inhalation	1	
Tuberculosis from infancy		2 (3%)
Foreign body		1
		60

diagnostic possibilities to recognize it. Apparently neither negative operative nor negative roentgenological findings can rule out sinusitis. We refer to Hueneken[3] who, in 118 patients, found agreement of the two methods of examination in 60 per cent, disagreement in 40 per cent. He reports positive roentgenological findings without obtaining pus on operative examination in 33 per cent of his patients while the reverse, of a negative roentgenogram but positive operative examination, was true

[3] Amer. Jour. Dis. Child., 1931, *42*, 716.

in only 7 per cent. It seems that, like pulmonary disease, sinus involvement cannot be ruled out without a roentgenological examination. Therefore, roentgenograms of the chest, as well as of all the sinuses, are a requirement in the diagnosis of bronchiectasis and its associated conditions. Although the treatment of sinusitis cannot be expected to influence existing bronchial dilatations except, perhaps, in the small child, it definitely is a prerequisite for the attempt to arrest the process.

It is not the purpose of this paper to go into the symptomatology in any detail. Table 4 is presented merely to point out a few discrepancies between findings and current beliefs in medical practice. As almost all

TABLE 4

Bronchiectasis

Symptoms

Cough: Mild	0		Continuous	55
Moderate	21		Seasonal	5
Severe	39			60
	60			

Expectoration:			Sputum:	
None	0		Mucous	1
Little	7		Purulent	59
Moderate	14		Odorous	28 (47%)
Copious	39			
	60			

Haemoptysis: 19 (in 7 of these, blood-streaked sputum only)
Dyspnoea of some degree: 14
Fever: 16 (usually little and intermittent)

patients presented in the series had advanced bronchiectasis, the pulmonary symptoms were in no case slight. The general condition was poor in 25 per cent and just fair in the rest. Copious expectoration, however, occurred only in about two-thirds and odorous sputum, supposedly an outstanding characteristic of the condition, in less than one-half. Haemoptysis occurs frequently enough to be eliminated as a criterion in the differentiation of bronchiectasis from other pulmonary diseases, especially tuberculosis.

Bronchiectasis is essentially a disease of the lower lobes of the lung, which are most easily accessible to drainage from above. One or both lower lobes were involved in 54 out of 60 patients. Of single lobes, the left lower one was the one most frequently affected, namely, in 33 per

cent. If the latter group is added to the bilateral involvements, the left lower lobe was found to be bronchiectatic in 80 per cent of the patients. The retrocardiac portion of this lobe is the only part of the lungs where, without a radiopaque examination, even extensive bronchial dilatations may be missed roentgenologically. There is no good explanation to offer for the frequent involvement of this part of the lung. One could venture the conjecture that in bilateral, infantile bronchiectasis the dilatations elsewhere in the lung may show a tendency toward readjustment and disappearance after elimination of the exciting cause, while in the retrocardiac space this process is prevented by adhesive, pericardial pleuritis in combination with the heart action.

TABLE 5

Bronchiectasis

Site of Involvement

Right lung only		12
Upper lobe	0	
Middle lobe	2	
Lower lobe	6	
Middle and lower lobes	4	
Left lung only		20
Upper lobe	0	
Lower lobe	20	
Both lungs		28
Both lower lobes	28	
		60
Left lower lobe involved in 48 patients		(80%)

The therapy of bronchiectasis, until very recently, has been a disappointing chapter. Conservative procedures, such as general management, postural drainage, bronchial lavage, and bronchoscopic treatment, are palliative and any improvement is merely symptomatic. By meticulous care the progressive bronchial dilatation will, at best, be delayed, and the patient remains an easy victim for complicating or intercurrent disease. Collapse therapy has, on the whole, proved itself a failure. During the past few years very encouraging results have been reported from removal of bronchiectatic lobes. Lobectomy, however, requires (or in our opinion should require) a unilateral, or practically unilateral, involvement. In suitable cases the patient should be urged to submit to operative treatment.

The most important of all therapies, prevention, has been sadly neglected up to now. There is a good deal of parental negligence toward chronic, upper respiratory infection and moderate chronic bronchitis in children. The threat of a severe and permanent bronchial damage is practically unknown. People to whom tuberculosis is a household word have not heard of bronchiectasis, although physicians recognize it as, next to neoplasm, the most hopeless pulmonary disease as far as restitution of the diseased part of the lung is concerned. Great concern is felt when a child aspirates a foreign body, considerable attention is paid nowadays to impairments of the respiratory function from allergic causes, but the danger of the slow and continuous drainage of infected material into the bronchial passages and of the resulting bronchitis is under-

TABLE 6

Bronchiectasis

Therapy and Results‡

THERAPY	CURED	SYMPTOMS IMPROVED	UNIMPROVED	WORSE	DIED
General therapy, postural drainage	1	14*	4	4	3
Collapse therapy:					
Pneumothorax		1			
Phrenic operation		2			1
Phrenicotomy plus thoracoplasty		1			
Lobectomy	1	3†			1

* Symptomatic improvement was mostly slight.

† Minor bronchiectasis of opposite lung.

‡ 24 patients were not under sufficient observation to judge results.

estimated. And yet, it is, as we have seen, the chief causative factor in bronchiectasis, especially of the extensive and life-threatening variety. We should venture to say that in proportion to the growing recognition of the rôle which chronic sinusitis has in this disease, its occurrence should decrease. At present it needs to be looked upon as a public health problem requiring the efforts of agencies concerning themselves with public health. By propaganda, examination of the sinuses, including a roentgenogram, should be suggested to the parents and guardians of all children in whom no other cause of a chronic cough can be found. The competent treatment of sinus conditions should be urged.

In Chicago and the neighboring sections of the Great Lakes region with its high atmospheric humidity, we often feel compelled to recom-

mend a change of climate for sinusitis, preferably to the dry Southwest. Even bronchiectasis of minor degree is favorably influenced there, while patients with extensive lesions will hardly be helped measurably. Other authors have reported little benefit from climatic changes. To us it seems that a permanent change of domicile—hardly ever a temporary one—can yield lasting results. While many of us in the East and Middlewest rather frown upon the westward movement of patients with active tuberculosis and believe that tuberculous cavities should be closed at home, we feel that we should hail the drier regions of the country as a land of hope for those who have, or are threatened with, chronic, nonspecific infections of the respiratory tract.

The suggestion has been made to look upon and discuss all the nonspecific lung infections, especially bronchiectasis and lung abscess, as one great group of suppurations with various degrees of interrelation. To the pathologist this must be a tempting thought, but while it is true that an abscess may follow bronchiectasis and some degree of bronchial dilatation frequently remains following a lung abscess, and while the pathological changes almost always indicate a series of events comprising this whole field (in patients, by the way, who come to autopsy), the clinical events in both diseases require a strict differentiation into two entities. The time element alone makes this necessary. Bronchiectasis stands out through the great chronicity of all events, from the beginning to the acute end from lung abscess or pneumonia, while lung abscess nearly always begins as an acute involvement. Its chronicity occurs from the lung's inability to rid itself in time from infected material, while the bronchiectatic lesion is largely produced by the very process of chronic elimination. Of the fifty lung abscesses presented in our series, nearly all entered what we might term the chronic stage of localization and wall formation. It is not possible to give a definite time after which an abscess should be called chronic, but cursorily we can estimate that it becomes so after somewhat more than one to two months of duration of illness. The average duration until death or recovery was slightly over four months. Table 7 shows the distribution of the aetiological factors, which were equally divided between aspiration from extrapulmonary infections and other causes. We make no reference to the details of symptomatology, systemic or pulmonary, except for stating that they depend upon the virulence of the invading microörganisms and the local tissue response but chiefly upon the degree of bronchial connection with the abscess and the resulting possibility of spontaneous drainage. Nor

does it seem necessary to discuss physical findings since they can comprise the whole array of pulmonary signs if the involvement is large enough or multiple.

The differential diagnosis from tuberculosis depends upon the presence of a causative factor and upon the time during which the lesion develops, especially the period which excavation in the lung tissue requires, and, in addition, upon bacteriological findings. But the presence, or absence, or degree of any of these factors may not suffice for a clear differentiation.

TABLE 7

Lung Abscess

University of Chicago Clinics

Aetiology

(Average age: 43 years)

(1) Aspiration		25
Postpneumonic	6	
Posttonsillectomy	5	
Dental infection (extraction)	3	
Upper respiratory infection	10	
Traumatic perforation of esophagus	1	
(2) Haematogenous		11
Postoperative	9	
Extrarespiratory infection	2	
(3) Bronchial obstruction		12
Neoplasm (carcinoma, bronchogenic and metastatic)	10	
Foreign body	2	
(4) Direct extension (amoebic)		2
		50

Roentgenological examination likewise leaves us doubtful in many instances.

The primary aim of all therapy is to assure adequate drainage of the abscess. If medical treatment cannot accomplish this within a short enough period to avoid a bad lapse of the patient's general condition and the danger of aspiration into other parts of the lung, surgical drainage should not be delayed. On the other hand, a majority of abscesses which refuse to heal spontaneously subside quickly into localized, chronic lesions and can then be operated with greater safety than the acute progressive infections.

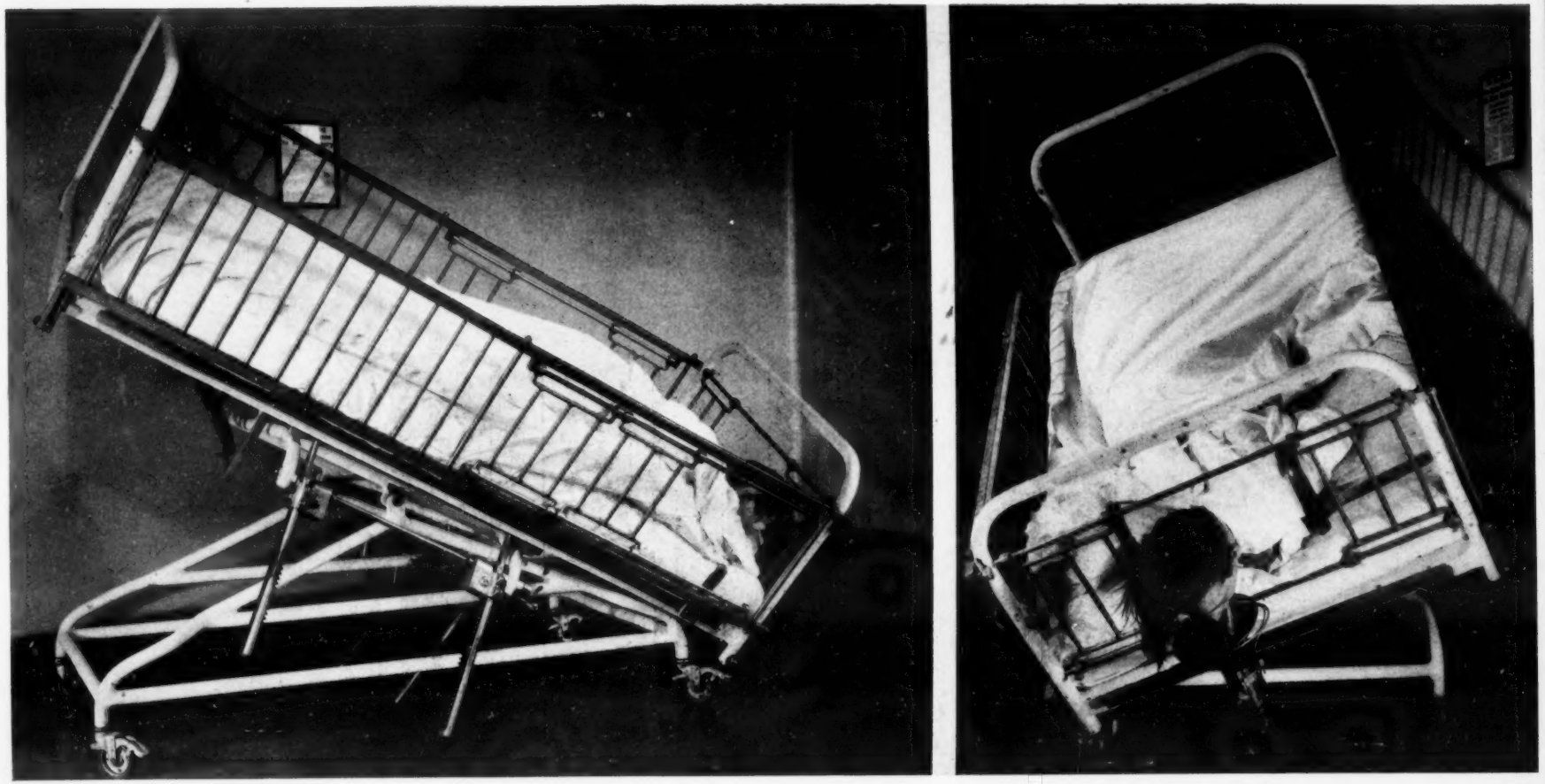

FIG. 1. Drainage bed. Specially constructed by the Scanlon-Morris Company, Madison, Wisconsin

For the medical treatment by postural drainage, we have been using with good results a specially constructed bed which can be tilted in all directions. For patients who were too weak to go into drainage position themselves, it has at times proved itself a life-saving apparatus.

The treatment of abscesses in our group was about equally divided between medical and surgical methods with about equal results. The mortality was 50 per cent, but even if the abscesses resulting from malignant neoplasm are eliminated, it still comes to 45 per cent. The postoperative, apparently embolic abscesses had a very high mortality, equal, in fact, to that of abscesses originating from intrathoracic neoplasm.

TABLE 8

Lung Abscess

Outcome of 50 cases

TREATMENT	RECOVERED	IMPROVED	UNKNOWN	DIED	TOTAL
Medical	10	3	2	13	28
Surgical	9		1	12	22
Total	19	3	3	25	50

Outcome of 47 cases with known results

AETIOLOGY	IMPROVED OR RECOVERED	DIED	TOTAL
Carcinoma	1	8	9
Nonmalignant aetiology	21	17	38
	22	25	47
Postoperative haematogenous abscess	1	8	9

This was probably due, in part, to the lesser ability of these lesions to find communication with bronchial passages but chiefly due to the fact that the patients were in a very weakened condition from extrapulmonary disease and operation.

Speaking of preventive measures, one can hardly go so far as to call lung abscess a public health menace. Nevertheless whatever education toward prevention is possible should be given, not only to the public, promoting prophylactic dental care, but to the medical and dental professions, warning against unwarranted and unskilful tonsillectomies and tooth extractions. The same efforts which can be directed against

upper respiratory infections with a view of guarding the people against bronchiectasis will help in the prevention of lung abscess.

We are not discussing the infrequent and rare chronic lung infections. A research hospital with a limited attendance of patients provides only scant material of this sort. Short mention, however, should be made of chronic pneumonitis, a term which has been used increasingly in recent years. It is difficult to give a definition of this condition (or group of conditions) which would justify setting it apart from what many of us recognize as pneumonic (and often recurrent) processes. They occur mostly as extensions or residuals of other bronchial or pulmonary involvements. Their chronicity, clinical manifestations, and roentgenological appearance can make the differential diagnosis from tuberculosis difficult.

As an outstanding representative of the group of chronic pneumonic lesions, lipoid pneumonia is found in an increasing number of patients. It results from the aspiration of fatty substances, especially oils which are applied to the respiratory tract for reasons of therapy. Here, too, is a field for preventive education.

PATHOLOGY OF CHRONIC NONTUBERCULOUS INFLAMMATIONS OF THE LUNG[1,2]

B. S. KLINE

Recently, in one of three concise articles on the subject, Austrian (1) aptly likened the exploration of pulmonary diseases to the identification of trees and other vegetation in a forest. Similarly Marshall and Brunn (2) reviewing the bacteriology of lung abscess in 1933 remarked that the various relevant contributions left many stones unturned. The answer to the problem they felt was probably twenty years off rather than two.

While much clarification of pulmonary inflammations remains for the future, it is likewise true that in the past twenty years careful clinical, surgical, roentgenographic, bronchoscopic, bronchographic, histopathological and especially bacteriological studies of thousands of cases have aided greatly in a clearer understanding of diseases of the lung. Furthermore, experimental studies in animals have also added much relating to aetiology and pathology. Perhaps the most outstanding recent advance has been the determination of the important rôle, in many cases, of oral spirochetes, fusiform bacilli and vibrios (Miller-Vincent microorganisms) in the causation of necrotizing bronchopulmonary lesions.

Among the excellent reviews of the recent progress are those of Graham, Singer and Ballon (3), Heuer, Andrus and Taylor (4), Maxwell (5) and Smith (6). A brief description of the pathology of common chronic inflammations of the lung other than tuberculosis follows.

BRONCHIECTASIS

Among the recent valuable contributions to the aetiology, pathogenesis and pathology of bronchiectasis are those of Carr (7), Brauer (8), Wiese (9), Opie (10), Schneider (11), Eggers (12), Thorpe (13), Hedblom (14), Boyd (15), Moll (16), Smith (6), Erb (17), Miller (18),

[1] Read as part of the Symposium on *Chronic Nontuberculous Infections of the Lung* at the joint session of the Pathological and Clinical Sections at the 34th annual meeting of the National Tuberculosis Association, Los Angeles, California, June 21, 1938.

[2] From the Laboratory Department, Mount Sinai Hospital, Cleveland, Ohio.

Graham, Singer and Ballon (3), Moolton (19), Rabin (20), and Weinberg (21). An excellent review of the subject with illustrative gross and photomicrographs of the pathological changes is that of Graham, Singer and Ballon (3).

The essential abnormality in bronchiectasis is the absence, atrophy, damage or destruction of elastic and muscular tissues of the bronchial wall. There is usually severe inflammation of the various coats at first, with damage or destruction of the elastic and muscular tissues. Sooner or later, as the process becomes chronic, complete destruction of a portion or all of the bronchial wall for a variable distance results and usually there are associated inflammatory and necrotic changes of the regional pulmonary parenchyma. In children, staphylococci, in adults the Miller-Vincent microörganisms, are frequently the causative agents responsible for the necrotizing changes.

In some cases, however, little or no inflammation of the wall is detectable and the principal lesion appears to be atrophy of the elastic and muscular tissues. In some of these cases there may be marked regional atelectasis or chronic peribronchiolar, peribronchial or regional interstitial pneumonitis with fibrosis. In these conditions, peribronchial lymphangitis aids in the rapid regional spread of the inflammation. Dilatation of weakened bronchi apparently follows as a result of the intrabronchial pressure of normal or forced respiration, of coughing and also whenever abundant exudate accumulates in the involved bronchi. This process as well as the subsequent further damage of the walls is favored by the obstruction of an aspirated foreign body or by any lesion producing stenosis of the lumen.

Depending upon the location, extent and severity of the process, cylindrical, fusiform or saccular bronchiectasis results. Ballon and Ballon (22) describe five main radiological types as demonstrated by lipiodol, (*1*) grape-like, (*2*) clubbing, (*3*) cylindrical, (*4*) saccular, and (*5*) bead formation. Mixed forms may involve the same lung. Usually the lesion is confined to one lobe at first, most frequently a lower lobe, and may be limited to terminal, tertiary, secondary or primary branches, or involve tertiary and secondary branches or tertiary, secondary and primary branches. Wiese (9) in 114 cases in children found the incidence as follows: left lower lobe 50, right lower lobe 11, both lower lobes 41, central portions 7, right middle lobe 2, miliary 2, left upper lobe 1.

Congenital bronchiectasis: Cases of this type are rarely observed. In

all, the essential lesion is some anomaly of bronchial or pulmonary development. In one form, as pointed out by Miller (18), the very early antenatal interference with bronchial branching and terminal bud formation is followed by the distension of a stem bronchus, and one or a few large cysts develop in place of an entire lung. At times variously sized multilocular cavities, with or without open connections with large bronchi, are formed. In another type many to innumerable small cyst-like structures are observed toward the periphery of the lung involving terminal bronchioles. Again, dilated bronchi may be found associated only with congenital atelectasis. Certain bronchopulmonary anomalies may be carried without symptoms until sometime in adult life.

Acquired bronchiectasis: Bronchiectasis is almost always an acquired disease. In children it most commonly follows bronchopneumonia or bronchitis complicating whooping cough, measles and influenza or results from the aspiration of an infected foreign body or of exudates from lesions in the upper respiratory tract. In the cases following influenza, early lesions show characteristic necrotizing changes involving especially the elastic tissue of alveoli, air sacs, atria, alveolar ducts and respiratory bronchioles and also show more or less regional inflammatory exudate. Later, dilatation, rupture and cavities with delicate walls occur in the distal bronchioles and regional lung parenchyma and the inflammatory changes become more pronounced.

In cases of bronchiectasis in children, as shown among others by Thorpe (13), Boyd (15), and Erb (17), a great variety of aerobic mouth microörganisms including diphtheroids, streptococci, *M. catarrhalis*, pneumococcus, *B. influenzae* and staphylococci become entrenched in the lower bronchopulmonary tract, increase enormously in number, bring about a severe bronchitis especially of the smaller branches and when they produce sufficiently marked degenerative and necrotic changes of the elastic and muscular tissues of the wall, cylindrical or fusiform bronchiectasis (hypertrophic type) results. Sooner or later, as the process becomes chronic, complete destruction of a portion or all of the bronchial wall for a variable distance results and usually there are associated inflammatory and necrotic changes of the regional pulmonary parenchyma. In children, staphylococci, in adults the Miller-Vincent microörganisms, are frequently the causative agents responsible for the necrotizing changes. Following the destructive changes, granulation tissue formation and epithelial relining occur. Not infrequently bronchopulmonary spaces are relined by tall columnar epithelium apparently

springing from some intact portion of the regional bronchus. In some cases, stratified squamous epithelial lining of the spaces occurs. Under certain circumstances there is proliferation of smooth muscle tissue apparently from the walls of large blood vessels which form a part of the wall of the bronchopulmonary cavitation as well as from other sources. Cartilage formation in the walls of large, old, healed areas of bronchopulmonary necrosis reaching at times to within a few millimetres of the pleura has been observed. Although in some cases of bronchiectasis there is damage of bronchial walls only of variable degree and extent, in many others the bronchiectasis is apparent only and the process in reality consists of active, healing and healed areas of bronchopulmonary inflammation and necrosis. Many of the healed areas show structures which greatly resemble dilated bronchi and which reach at times almost to the pleura.

In all these cases, the bronchial exudate, although not infrequently very abundant, has no appreciable odor. It is whitish or yellowish, purulent or mucoporulent and contains some or all the microörganisms described above.

Similar bronchial lesions occur in adults after influenza, various upper respiratory infections or after a primary bronchitis. An excellent description of the pathology and pathogenesis in the influenzal cases is given by Wolbach, Goodpasture and Burnett, and Opie (10).

In some cases, the bronchitis is much less severe and limited to a catarrhal inflammation of the mucosa. Nevertheless it is considered that there is occasionally sufficient atrophic or degenerative change of the elastic tissue of the wall to result in bronchiectasis (atrophic type). The dilatation may persist even after the inflammation of the mucous membrane has resolved. Similar changes may follow mild peribronchial inflammations.

In adults and children, the saccular type of bronchiectasis is usually the end result of a focal necrotizing bronchopulmonary lesion. In adults, tuberculosis and gangrene are more frequently the primary conditions than abscess. In children, on the other hand, tuberculosis and abscess are the antecedent lesions more often than gangrene.

In the stages of necrosis and of cavitation, the pulmonary involvement is readily discernible but in the stage of healing and of repair and particularly long after the complete cessation of the local process, the lesion appears to be a saccular bronchiectasis. In reality, however, it is a saclike bronchopulmonary cavity lined by a wall which comes more and more to look like that of a dilated bronchus.

The bronchial lesions observed postmortem at Mount Sinai Hospital of Cleveland in 39 cases of pulmonary gangrene varied from simple mild inflammation of the mucous membrane to complete destruction of the bronchial wall. In the milder lesions, the exudate in the lumen and in the wall showed nothing characteristic except that oral spirochetes, fusiform bacilli and vibrios (Miller-Vincent microörganisms) were present as well as the usual oral aerobes. In more advanced cases of this type, on the other hand, ulceration of the mucosa and destruction of elastic and muscular tissues and even of cartilage were observed. In some cases of gangrene there was complete necrosis of portions of the inflamed bronchial wall and of the inflamed regional parenchymatous tissue. The lesion formed thereby was bronchopulmonary cavity rather than bronchiectasis.

Lesions such as those described above, especially when of long duration, often harbor the Miller-Vincent microörganisms and various bacteria in symbiosis in the form of small white, yellow or brownish balls and these are not infrequently expectorated in such cases. The bacterial granules are similar to those which form in tonsillar crypts and dental cavities.

The various bronchial lesions described above depend in considerable part upon the number, type and virulence of the causative microörganisms. Another factor of importance in inflammations of the lung, as elsewhere in the body, is the state of the involved tissue. This is strikingly shown in cases of bronchial asthma. Whereas repeated inhalations of pollens, dusts and other allergens produce negligible reactions in the bronchial walls of the majority of individuals, in highly sensitive allergic persons, on the other hand, they bring about repeated severe inflammations. Not only is there abundant tenacious mucopurulent exudate in the lumen and considerable distension of mucous glands, but also considerable oedema, round cell infiltration and haemorrhage of the mucosa.

CHRONIC PNEUMONITIS

Chronic pneumonitis and induration are most frequently associated with chronic suppurative and chronic gangrenous processes. At times also, following postinfluenzal pneumonitis caused by a great variety of mouth microörganisms, there may be organization of alveolar and interstitial exudates with repeated extension of the pneumonitis from active or healing foci. The inflammations are exceedingly varied and the

severity, to a considerable degree, depends upon the causative bacteria acting singly, in combination and in symbiosis.

A specific type of serious chronic pneumonitis first reported by Laughlen (1925) (23) and Pinkerton (1927) (24) is that which follows the aspiration of oils and fats, especially mineral oil and its medicated forms, animal oils and fats, such as codliver oil and milk. Early lesions show numerous macrophages containing oil droplets in the involved alveoli of the lung. In places also, numerous neutrophilic polymorphs are present and here the picture resembles that of ordinary bronchopneumonia. Laughlen thought that this pneumonitis was "septic" and that the paraffin oil lowered the resistance of the tissue or carried the infection from the nose or throat. Pinkerton was uncertain as to whether the areas of severer pneumonitis were due to infection or to chemical irritation. Later lesions show extensive fibrosis within alveoli and alveolar walls; there are small oil droplets within macrophages and large oil droplets surrounded by giant cells. The late lesion resembles the paraffinoma produced by subcutaneous injection of oil. Metastatic oil deposits have been described in bronchial lymph nodes, spleen and kidneys. In the two latter organs, severe arteritis dependent upon arrest of granular lipoid material in the *vasa vasorum* has been reported (25).

In 1928 Pinkerton (26) reported the results of single intratracheal injections of vegetable, animal and mineral oils in rabbits and dogs. Reactions of from 1 to 115 days were studied. It was found that the vegetable oils underwent no appreciable change in the lungs and caused no appreciable reaction. Mineral oil on the other hand emulsified quickly and was taken up by phagocytic cells and consolidation produced. In these cases, giant cell formation and fibrosis were slight at the end of the second or third month. Pinkerton found that the animal oils (milk fat, rabbit fat, codliver oil and lard oil) caused marked fibrosis and giant cell formation within a few days. The necrosis often observed in the region of inflammation produced by these oils was apparently due to liberated fatty acids.

Since the original publications of Laughlen and of Pinkerton a hundred additional cases of lipoid pneumonia have been reported (Ikeda (27)).

In a case reported by Young, Applebaum and Wasserman (25) from Mount Sinai Hospital of Cleveland, all stages of the process were observed at autopsy in the lungs of a white female, age 46 years, who for over three years before death had frequently taken mineral oil by mouth and almost a quart of codliver oil in the past year. The right lung was found consolidated almost every-

where, in part dark red, suggesting haemorrhage or early pneumonitis, in part grayish in color and resembling the gray hepatization of lobar pneumonia. The lesions in the left lung were of a very different character. In the lower lobe there was a circumscribed, roughly spherical, firm gray area about 10 cm. in diameter and elsewhere in the lobe a similar circumscribed hard nodule about 2 cm. in diameter. These lesions on gross inspection, as in certain cases reported previously by others, suggested metastatic carcinoma nodules. (The patient had had a radical mastectomy three years before death with removal of a comedo duct carcinoma 2.5 cm. in diameter. No metastases in the axillary lymph nodes were found.)

Microscopical examination of the most recent pulmonary lesions in this case showed extensive parenchymatous haemorrhage. In places there was some fibrin deposit. In quite a number of alveoli also there were a few to many macrophages, containing small oil globules. Elsewhere there were free oil droplets (scarlet R). The oil present, however, was much less abundant than in the sections from the diffuse gray consolidation regional to the haemorrhagic areas. These (stained by scarlet R) showed abundant finely emulsified orange-stained lipoid material especially within alveolar walls and at the regional alveolar borders. Present also in the alveoli and in the vessels of the alveolar walls were numerous neutrophilic polymorphs. There was fairly abundant fibrin present in the alveolar exudate. Sections stained by the Gram method, carefully examined, revealed no microörganisms whatever and it was concluded that the pneumonitis was a purely chemical one. In some sections abundant finely granular lipoid material was observed in the thickened alveolar walls themselves, as described by Pinkerton.

Microscopical examination of the circumscribed firm lesions in the left lower lobe showed them to be strikingly different than the diffuse pneumonitis in the opposite lung. In the sections stained by scarlet R, numerous orange lipoid globules were observed, many in macrophages and where large (in places over a 100 μ in diameter) surrounded by giant cells. Most of the giant cells were situated toward the periphery of the alveoli. Smaller globules were also observed within the alveolar walls. In these sections, and better still in hematoxylin and eosin stained preparations, abundant fibrous granulation tissue was observed everywhere within the alveoli and alveolar walls. In places within alveoli there was amorphous granular material apparently necrotic exudate and necrotic granulation tissue. In many places alveolar markings were completely obliterated.

Lipoid masses were also found in the regional lymph nodes and spleen, as described by Pinkerton. In addition, Young, Applebaum and Wasserman found extensive metastatic lipoid masses in the kidneys. In scarlet R preparations, finely granular orange-stained lipoid material was especially abundant in the vessels of the glomerular tufts; in hematoxylin and eosin stained sections

the picture was that of severe chronic nephritis with the majority of glomeruli showing degenerative and proliferative changes of varying degree, in general considerable. In places there was complete necrosis and considerable round cell infiltration. There was also some involvement of the regional interstitial tissue. In addition, many medium sized and small arteries showed degenerative changes of the walls and prominent round cell infiltration resembling the picture in periarteritis nodosa. The lipoid deposits in the spleen involved the small and medium sized arteries as in the kidney. The apparent cause of these lesions was the presence of finely granular lipoid material (scarlet R and osmic acid stained) in the *vasa vasorum*. These observations suggest the possibility that in periarteritis nodosa also the lesions are produced by the arrest of a granular material (allergenic) in the *vasa vasorum* of the involved arteries.

ABSCESS OF THE LUNG, GANGRENE OF THE LUNG

More serious than bronchial diseases and various inflammatory consolidations of the lung are the necrotizing and ulcerative lesions of gangrene, tuberculosis and abscess. At the present time, the various types of pulmonary tuberculosis are readily recognized. Gangrene and abscess of the lung however are still not universally considered as separate entities.

Over a hundred years ago, Laennec (28) on the basis of careful clinical and pathological observations clearly differentiated between abscess and gangrene of the lung. In addition to the presence of certain distinguishing auscultatory signs and a difference in constitutional reaction, the sputum in abscess was observed to be coherent or viscid and yellowish, whereas in gangrene it was characteristically diffluent, of various shades of gray, green or brown and penetratingly foul-smelling. Furthermore the pulmonary lesions themselves differed greatly. Abscess was a collection of yellowish pus, whereas gangrene was a spreading, friable, ragged, green or brownish focus, emitting a penetrating foul odor.

In spite of the fact that this adequate differentiation between abscess and gangrene of the lung is further supported by strikingly different histopathological changes and by the constant finding of decidedly different types of bacteria in the two lesions, the majority of investigators and reviewers still confuse these two diseases.

Pilot and Davis (29), Lambert and Miller (30), Smith (6), Varney (31), Flick, Clerf, *et al.* (32), Bucher (33), Marshall and Brunn (2), and others, have reported finding spirochetes, fusiform bacilli and vibrios in cases of lung abscess and Pilot and Davis (29), Smith (6), Crowe and Scarff (34), Allen (35), Hedblom, Joannides and Rosenthal (36), Her-

mann and Cutler (37), Van Allen, Adams and Hrdina (38), Lambert and Weeks (39), have reported the experimental production of lung abscess in animals with these microörganisms. It is probable, as pointed out by Heuer (40) in a recent critical analysis of the literature, that the lesion in some of these cases was gangrene and not abscess.

The following (translated) statement of such a careful observer as Laennec (28-b) is still worthy of mention and still timely.

> Notwithstanding the opinion of the ancients, and the ideas commonly prevalent among medical practitioners relative to abscess of the lung, called also vomica, there is no organic lesion so uncommon as a bona fide collection of pus in the pulmonary tissues.

Lest the enthusiasm for Laennec's careful observations and his vivid descriptions be misinterpreted, a final relevant quotation from his translated work (28-c), not at all subscribed to, is given:

> It may be here stated that the intimate structure of all the organs is almost, equally with that of the lungs, beyond the reach of our vision and instruments of research, and that consequently nothing is certain in pathological anatomy beyond the well-defined lesions which fall immediately under the cognizance of our senses, and which alter the structure of an organ in a manner obviously incompatible with the discharge of its functions.
>
> If these rules be departed from,—if the causes of severe diseases be sought for in microscopic alterations of organs, it is impossible not to fall into absurd conclusions; and pathological anatomy, as well as that of the healthy body, cultivated in this manner would soon lose the rank they hold amongst the physical sciences and be converted into a vast field of hypotheses founded on optical illusions and speculations of no practical utility in medicine.

Although it is hard at times to distinguish between abscess, putrid abscess and early gangrene with the microörganisms both of suppuration and of gangrene present, or with a flora characteristic of abscess changing to one of gangrene or vice versa, this difficulty does not justify the consideration of these two diseases as one entity. It cannot be stressed too much that pyogenic microörganisms never produce gangrene, whereas the fully developed and characteristic lesion caused by spirochetes, fusiform bacilli and vibrios is not abscess but gangrene.

Since acute cases of pulmonary gangrene do not respond well to the treatment for abscess but are frequently cured by arsphenamine therapy, the differentiation between these two diseases is imperative.

Pathogenesis: The majority of observers and investigators believe

that the lesions in pulmonary gangrene and localized lung abscess, including those that develop after operation, are caused by the aspiration into the lungs of microörganisms from the upper respiratory tract. A number, however, believe that in most pulmonary conditions, especially in the postoperative group, the microörganisms reach the lung through the blood-stream.

Cutler, Schlueter, Weidlein and Holman (41) and Fetterolf and Fox (42), among others, present the clinical and experimental evidence for the origin of postoperative abscess by embolism and their belief that reduction of trauma at the operative site by the surgeon may prevent such a complication.

Evidence that pulmonary gangrene and lung abscess, including the lesions following operation, follow aspiration of the causative microörganisms from the mouth and can be prevented by proper oral hygiene or therapy is given in a former article (43).

While cases of multiple embolic pulmonary abscesses, associated with areas of suppuration elsewhere in the body and frequently with bacteraemia (usually staphylococcal) are of common occurrence, cases of unequivocal embolic pulmonary gangrene are rare, and most frequently follow from putrid puerperal infections, gangrenous decubital ulcers and gangrenous tumors of the intestines and female genitalia.

A series of cases of abscess and of gangrene of the lung, observed with Dr. S. S. Berger over a ten-year period, was reported a few years ago (44). The study included 55 cases of pulmonary spirochaetosis, better designated Miller-Vincent's infection of the lung, 12 cases of localized bronchogenic pulmonary abscess and 23 cases of embolic pulmonary abscesses. In 39 of the 55 cases of pulmonary spirochaetosis the lesion was that of fully developed gangrene. Gangrene was observed more than three times as often as bronchogenic abscess and was more than four times as common in adults as in children. Bronchogenic abscess, on the other hand, was observed twice as frequently in children as in adults.

Embolic pulmonary abscess: The embolic abscesses observed at autopsy in this series were multiple, usually small (from 5 to 15 mm. in diameter) and more or less spherical, occurring in a number of lobes and associated with areas of suppuration elsewhere in the body (in the kidneys, in the myocardium and occasionally in the brain). The lesions were grayish or yellowish and soft or viscid, with little or no odor. In a few cases in which the lesions were numerous, they were coalescent in places.

Early lesions were reddish and more coherent. In some cases there was infarction and suppuration, with the lesions more or less wedge-shaped, larger than embolic abscesses and situated along the lower borders of the lobes. A number reached and involved the pleura. Smears and cultures showed the staphylococci. In sections stained by the gram method, abundant microörganisms were observed in and about occluded blood vessels. The involved pulmonary tissues were necrotic and usually completely replaced by pus.

Bronchogenic lung abscess: In contrast to the postmortem picture in embolic abscesses, the suppuration in cases of bronchogenic abscess was found confined to the lung only. Multiple lesions were occasionally found, but the process was usually limited to one or more foci in one lobe. The lower lobes were most frequently involved. The lesions in general were larger than embolic abscesses and associated with areas of bronchopneumonia.

The local lesion was usually several centimetres or more in size, irregular in shape, owing to the coalescence of foci, and surrounded by inflamed lung tissue. The involved area was soft or viscid, gray, yellow or yellow-brown, with little or no odor unless the microörganisms of gangrene were present. Early lesions were reddish and hardly distinguishable from areas of pneumonia. Well developed lesions showed complete necrosis of inflamed lung tissue and replacement by innumerable intact and degenerating pus cells. Smears and cultures showed the pyogenic microörganisms, usually staphylococci, at times other oral cocci were also present. In one case colon bacilli, in another *B. pyocyaneus*, were found associated with staphylococci.

Sections of early lesions stained by the gram method showed numerous clusters of staphylococci in the bronchial branches and alveoli whereas the regional blood vessels were uninvolved.

Chronic bronchogenic abscess: The majority of bronchogenic abscesses in this series were of the acute type and of comparatively short duration. Some, however, remained unhealed and were chronic. A postmortem study of the few lungs with such genuine chronic abscess observed in the past suggests the following pathogenesis: succeeding the pneumonitis and subsequent suppuration caused by pyogenic microörganisms, the involved area, alone or following coalescence with similar areas, undergoes ulceration as the viscid material is evacuated. The resultant cavity is lined by inflamed lung tissue. In some portions where the process is more or less arrested, granulation tissue forms and is lined in

places by bronchial or modified bronchial epithelium. In certain areas, however, the pyogenic microörganisms cause further inflammation and suppuration and, with the evacuation of the pus, the cavity enlarges. Such areas may subsequently undergo partial or complete healing. The extension by inflammation, consolidation, necrosis and cavitation of bronchogenic abscess is decidedly less than occurs in gangrene, and the suppurative disease accordingly is a milder one. Pleural involvement is frequent in these advanced cases and there may be empyema or pyopneumothorax.

Pulmonary gangrene: In contrast to the grayish or yellowish suppuration of abscess with little or no odor, the lesion in gangrene, as pointed out by Laennec, is ragged, brownish or greenish, and penetratingly foul-smelling. As in cases of bronchogenic abscess, gangrene most frequently involves the lower lobes. Not only is the process in gangrene much more severe locally than in abscess but the general intoxication is much more pronounced and the prognosis in untreated cases is much poorer. The cause of the color and the origin of the odor of gangrene are not known with certainty. The color may be due to alteration of the blood in the part. Varney (31) ascribes it to a melanin pigment produced by the *Bacillus melaninogenicum*. Furthermore Varney (31) and others report that this microörganism causes the foul odor of the process. Other observers however have incriminated spirochetes, vibrios or anaerobic streptococci in this activity.

Whereas the sputum in cases of abscess is viscid, yellowish, and has little or no odor and contains pyogenic microörganisms, in cases of gangrene it is usually thin, gray, brown or gray green, foul-smelling and contains oral spirochetes, fusiform bacilli and vibrios.

Sections stained with hematoxylin and eosin, by the Levaditi method and best of all by the Warthin and Starry method, show that the gangrenous process ordinarily appears first in areas of bronchopneumonia produced by ordinary mouth aerobes, as an intense colonization of Miller-Vincent microörganisms with associated regional necrosis of the exudate and of the fixed tissue. Following this, the lesion steadily enlarges because of extending bacterial colonization and necrosis. The lesion now is the fully developed and characteristic one of gangrene, grossly consisting of a friable, ragged, penetratingly foul-smelling, brownish or greenish area and microscopically showing innumerable oral spirochetes, fusiform bacilli and vibrios not only in the areas of necrosis but also at the advancing periphery. In a short time, ulceration occurs in necrotic

areas, contiguous ulcers coalesce, definite cavities form, and since no tissues are spared in the extension of gangrene, no large ridges or bridges of tissue ordinarily remain. In the cases with early ulceration or frank cavity formation, the contained material consists not only of necrotic lung tissue and exudate but also of innumerable bacteria (Miller-Vincent microörganisms and ordinary aerobic oral bacteria).

In a few fulminating acute cases, there was apparent intense primary colonization of Miller-Vincent microörganisms in scattered areas with resultant foul-smelling, dark green gangrene, ulceration and early cavity formation. In these cases especially, sections prepared by the Warthin and Starry method show strikingly the intense colonization of the Miller-Vincent microörganisms at the advancing edge of the process. In some areas of extension, innumerable oral spirochetes alone are present. The lesion well exemplifies a gnawing or devouring, implied in the term "gangrene." In hematoxylin and eosin and Nishimura stained preparations innumerable fine and coarse brown pigment granules are observed in places in the gangrenous areas. The granules suggest altered blood rather than melanin containing bacteria.

In the majority of cases of gangrene examined postmortem, the lesions were apparently subacute or chronic with areas showing partial healing and others showing recent extension of the inflammation and necrosis. In one case in another series, several healed cavities with intact epithelial lining were present, together with more recent gangrenous cavities, extensive pneumonitis and a terminal large area of gangrene of the brain. All the active lesions contained the characteristic Miller-Vincent microorganisms.

In the cases of gangrene of the lung reported, the pleura was frequently involved and not uncommonly there was gangrenous effusion. In some cases, there was associated pneumothorax.

Gangrene was found complicating active pulmonary tuberculosis in one case in this series and it has been reported involving degenerating tumors of the lung (Seecof (45)).

In some of the cases of bronchiectasis, chronic abscess and chronic gangrene of the lung, there was associated chronic pulmonary osteoarthropathy (drum stick or clubbed fingers, watch crystal nails).

Pneumonitis with Miller-Vincent microörganisms: There were six cases of this type reported in the series. The diagnosis was made clinically and corroborated by roentgenogram and sputum examination. The pulmonary involvement in these cases was probably similar to the early

lesions found in some cases of gangrene examined postmortem. In these there were areas of pneumonitis not unlike ordinary bronchopneumonia with some interstitial involvement. In some places the bronchopneumonic areas showed beginning degenerative and necrotic change of the cells of the exudate and of the fixed tissue. Smears and sections from intact and early necrotizing pneumonitis showed the characteristic Miller-Vincent microörganisms, together with a variable number of ordinary aerobic oral bacteria. In fairly early lesions, organization of the exudate in places was observed.

Miller-Vincent microörganisms: The spirochetes, fusiform bacilli and vibrios (Miller-Vincent microörganisms) (46, 47) of pulmonary gangrene are identical with those present in the interproximal spaces between the gums and teeth in practically all adults. The lesion most frequently produced by these microörganisms is a gingivitis. Exudate from such areas or elsewhere containing numerous or innumerable Miller-Vincent microörganisms may be aspirated into the lungs especially during sleep or during anaesthesia and produce gangrene. Other dangerous reservoirs of the microörganisms of gangrene are the foul-smelling white, gray, yellow or brown "granules" (colonies of aerobic and anaerobic bacteria in symbiosis) which form at times in dental cavities and tonsillar crypts.

The reported finding of oral spirochetes and fusiform bacilli in pulmonary gangrene by Rona (48) in 1905 was fully corroborated in 35 cases by Buday (49) (1910). Since then the Miller-Vincent microörganisms have been found in pulmonary gangrene by numerous observers in various countries.

In addition to the finding of the Miller-Vincent microörganisms in the gangrenous lungs, similar lesions in the lungs and elsewhere have been produced in animals with material from human pulmonary gangrene, Vincent's angina and ulcerative gingivitis and other lesions containing the Miller-Vincent microörganisms (50), also with cultures of these microörganisms and a streptococcus (51).

For the past ten years under the direction of Dr. M. B. Galvin, the dental service of Mount Sinai Hospital has given preoperative oral therapy to patients in the public wards. In a three-year period there were 9 postoperative pulmonary complications with 2 deaths in 5,078 treated service patients and 60 postoperative pulmonary complications with 18 deaths in 8,897 private untreated patients. The results give evidence that pulmonary infections, including those produced by Miller-Vincent microörganisms, may be prevented by proper oral hygienic or therapeutic measures.

I wish to acknowledge my appreciation of the assistance given in recent studies of bronchiectasis by Doctors R. Dominguez, H. Goldblatt, D. J. Rehbock and H. S. Reichle of Cleveland, Ohio.

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THE ROENTGENOLOGICAL ASPECTS OF NONTUBERCULOUS PULMONARY DISEASE[1]

J. J. SINGER[2]

It is difficult to discuss only the roentgenological phase of the examination without giving consideration to the history, physical signs and laboratory studies. The film alone may be misleading as to the true character of the lung lesions because similar densities are produced by many causes. Among the numerous nontuberculous lesions, bronchiectasis, abscess of the lung and benign and malignant tumors are the most important. The pneumonoconioses, pleural effusions, fungus infections and atelectasis are also important lesions to consider.

It is the purpose of this discussion to attempt to describe some of the important lesions found in the lung and to point out specific diagnostic criteria.

BRONCHIECTASIS

The shadows noted in the roentgen film in bronchiectasis without iodized oil may be very confusing (figure 1). In the lower lobes one usually finds dense band-like shadows extending from the hilum downward and outward. These bands are interspersed with air-containing spaces. Occasionally one sees a dense triangular shadow in the cardiophrenic space surrounded by brilliant or hyperaerated lung tissue. In the fluoroscopic examination one can better visualize this density. If the patient is given postural drainage this shadow may be less dense if much sputum is expectorated. Occasionally one finds fluid levels because air replaces the drained secretions.

Since the use of iodized oil for bronchography the positive diagnosis of bronchiectasis can be made even to its character.

There still seems to be some prejudice in certain localities concerning the use of the oil. This may be due to the fact that occasionally one sees an iodine reaction, such as rhinitis and sneezing. But these re-

[1] Read as part of the Symposium on *Chronic Nontuberculous Infections of the Lung* at the joint session of the Pathological and Clinical Sections at the 34th annual meeting of the National Tuberculosis Association, Los Angeles, California, June 21, 1938.

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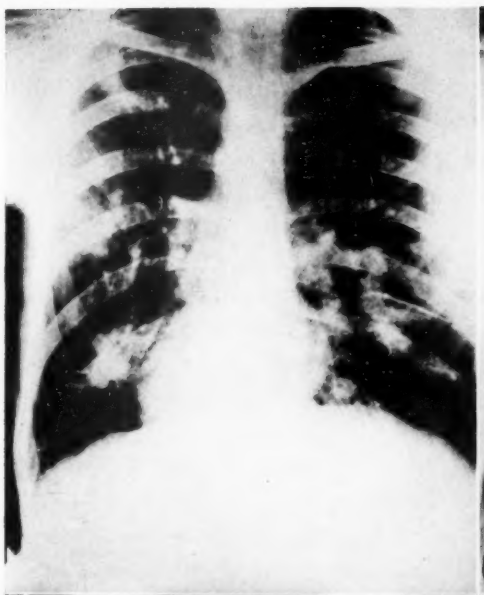

FIG. 1

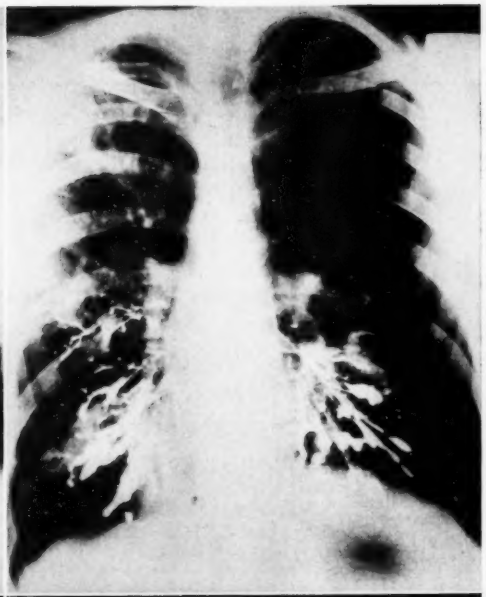

FIG. 2

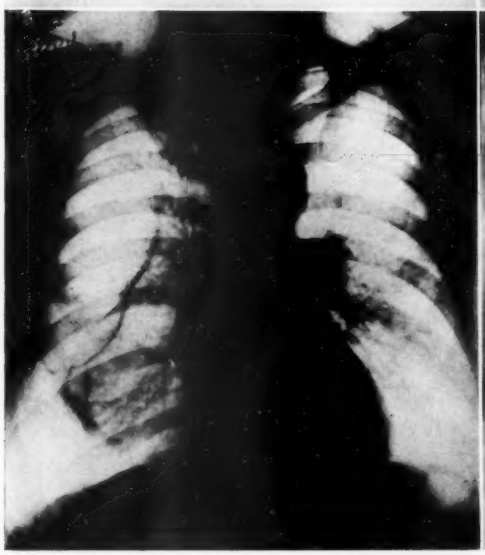

FIG. 4A

FIG. 4B

FIG. 1. Note the pulmonary markings throughout both lungs—in both bases the irregular densities suggesting bronchopneumonia.

FIG. 2. (Same patient) After injection of iodized oil into the bronchial tree one can definitely diagnose the lesion as bilateral bronchiectasis.

FIG. 4A. November 5, 1934. Shows large cysts in right lung, with possible small pneumothorax pocket in lower right costophrenic area.

FIG. 4B. 1930. Shows beginning cyst in right costophrenic angle. The development of several cysts, therefore, occurred since that time. Physical signs alone could not demonstrate this condition.

actions are so rare with large experiences that when a diagnosis is necessary for treatment the occasional reaction should not be considered too seriously.

The value of bronchography is evident when one considers that the bronchial tree rarely is noted as such, particularly the secondary and tertiary branches. When the latter are actually as large as normal primary branches the oil demonstrates them. The walls of the bronchi are coated with the oil; the oil does not fill the bronchi. The thin film of oil shows as a filled tube when the film is taken. But if it were possible to look into the bronchial tubes from above the patency of the tubes could be readily demonstrated.

What should one expect to see on the film following the instillation of the oil?

When an atelectatic bronchiectatic area is present, the tubes are widened, beaded, cylindrical, saccular or cystic. All of these types of lesions are demonstrated by bronchography (figure 2). The compensatory lung fields are seen with bronchi wide apart and not dilated and also on fluoroscopy one can see during inspiration how the bronchi spread out like a fan and close again on expiration. Thus the movements of the lung are easily demonstrable and many abnormalities can be noted.

The differential diagnosis of bronchiectasis is not always easy by the roentgen film unless due consideration is given to pathological conditions which often are complicating factors, particularly abscess formation and varying degrees of pneumonitis which may show densities.

It is necessary in the study of bronchiectasis to map out both lungs and also to have lateral views as well as posteroanterior or anteroposterior views. It has been observed that the best way to obtain a good lateral view of the bronchial tree is to inject only one lung at a time so that when lateral films are taken it will be known that the bronchial dilatations are in the lung injected. Several days should elapse before injecting the opposite side, in order that the oil injected previously will be coughed up.

No case of bronchiectasis should be considered as completely examined roentgenologically until both lungs have been injected.

This is particularly important since the medical treatment in most cases is at best only palliative and lobectomy is the only chance of a cure. But a lobectomy done, leaving portions of other lobes with bronchiectasis, not only serves no purpose but raises the mortality rate.

ABSCESS OF THE LUNG

This has no definite pattern in the film, but without the aid of roentgenological studies our information would be meagre.

There is, however, a marked difference to be seen in the film in abscess of the lung as compared with other lesions. The lesions may be single or multiple and the location may be either in one or both lungs. The presence of fluid levels which shift with position is most significant. In cysts of the lung one may find similar fluid levels, but the surrounding lung tissue in the latter condition is more normal.

There is usually more or less density of varying degrees about the lesions and often no air pocket is noted. In the early involvement one may only find a faint haziness around the hilum but this is not sufficient to make the diagnosis of abscess. But when the symptoms, such as severe cough, localized chest pain, with odor to breath, are present even the faintest localized shadows are important. If there is a history of tonsillectomy or nasal operation and occasionally even other operative procedures together with the symptoms described above, and a faint shadow, a diagnosis of abscess can be made.

The introduction of iodized oil in the abscessed areas, especially in acute cases, is contraindicated, but in a chronic form it may be used.

Bronchography demonstrates the finer bronchi to be closed or narrowed in an irregular manner. Occasionally one finds an area of density of the lung which is not outlined (a so called negative shadow). The reason for the presence of this type of shadow is that the very small bronchi are almost closed by the infection and the surrounding tissue may be atelectatic.

It is not unusual to find lesions of varying size, some of which may have fluid levels. In order to be positive that fluid levels are present, it is advisable to take a lateral supine film to see if the levels shift with change of position.

As the treatment of abscess of the lung is dependent on the detailed localization of the lesions, it is important to study cases carefully. Abscess of the lung is a frequent secondary condition to bronchiectasis, carcinoma and atelectasis from many causes.

Careful consideration of the clinical history, physical signs and bronchoscopic studies together with the roentgenographic studies will usually be sufficient to make a definite diagnosis.

CYSTS OF THE LUNG

Previously, a diagnosis of chronic lung abscesses and empyema and even bronchiectasis was made in cases of cysts. It is only in recent years that the entity of cysts of the lungs has been generally recognized.

The distinguishing features in the roentgen film are brought out by positioning the patient, postural drainage and at times injection of iodized oil either through the bronchial passage or through the chest-wall directly into the cyst cavity.

Many patients who have large cysts almost filling one or the other chest cavity, which at first seems to represent a pneumothorax cavity, will, on close study, show fine striations in the lung fields which do not conform to bronchial markings (figure 4). When iodized oil is directly injected into the cavity and the patient is rolled from side to side the oil adheres to the many trabeculae in the cyst cavity and the cyst walls and these are easily seen on the film.

Sometimes in addition to the cyst a pneumothorax is present which compresses the contralateral lung. In order to recognize these two conditions it is sometimes necessary to insert a needle connected with a manometer into the pleural space; the pressure changes as shown by the manometer will show whether the space entered is in the pleural cavity or in the cyst. Analysis of the aspirated air will also be of diagnostic value.

It is not unusual to see several cysts connected with a large bronchus and also find one or two of these that have no apparent connection. The fact that the cyst contains air shows that there must be some connection with the bronchus. The writer has had one case in which a hair-like connection was demonstrated between the bronchus and a very large cyst by the injection of iodized oil into the trachea.

Bronchiectasis is a frequent complication and can easily be demonstrated by iodized oil.

As the treatment of cysts is entirely surgical the roentgen ray study is the most essential factor in recognizing the true status of the patient. Thanks to the many improvements in roentgen ray techniques, few, if any, cysts of the lung will be overlooked.

TUMORS OF THE LUNG

Tumors of the lung are much more common than was suspected. In the reported statistics from various medical centres throughout the world, one can see the higher percentage of lung tumors now as compared

to twenty to forty years ago. In analyzing these figures it is apparent that our diagnostic acumen aided by roentgen ray studies has been of inestimable value in the recognition of tumors.

There is no characteristic picture to be seen in this condition so that many factors must be considered before making a positive diagnosis. Inasmuch as benign tumors may become malignant later, and also knowing that any growing mass within the chest cavity can only grow by compressing lung structures, we have considered benign tumors as clinically malignant and their surgical removal necessary.

Most benign tumors of the lung have a definite density and are usually round. The lung tissue about the mass looks normal except when the tumor has grown to such a size as to compress the lung.

Benign tumors arising from nerve tissue are called neurofibroma; from cartilage, chondroma; from bone, osteoma. Other tumors may appear to be in the lung but are actually only encroaching upon the lung. Good films of the spine and ribs frequently show the true condition. Iodized oil injection into the bronchial tree shows the tubes are merely compressed and not involved.

Malignant tumors on the contrary leave no differentiating shadows. The film may have the appearance of any other pulmonary involvement, particularly pneumonic consolidation, atelectatic lung or even fluid (figure 3).

The surgical approach to the treatment of cancer of the lung can only be advanced when the diagnosis of pulmonary malignancy can be made early and surely before metastases have taken place.

For that reason patients who have passed the fourth decade should be under suspicion of malignancy when symptoms of pain in the chest, cough, slight haemoptysis and dyspnoea present themselves.

The fluoroscopic studies are most important as one can, by changing the position of the patient, see whether a shadow is anterior or posterior in position. By doing a diagnostic pneumothorax, especially when fluid is present, one can see how much of the shadow is mass and how much is due to fluid (figure 3).

It is also possible by fluoroscopic study to see the best position in which to place the patient for the films. A change of position of twenty to forty degrees in making the film may be the deciding factor in recognizing the true condition. This is particularly so when looking for small metastatic masses along the axillary borders of the lungs.

Stereoscopic films are sometimes useful, but the writer has used films

taken in two directions—posteroanterior and lateral decubitus. A shifting fluid level or air pockets denote fluid and cavities.

Kymographic studies which show the movements of the heart and diaphragm give important information. A paralyzed diaphragm or adhesions to the pericardium are easily noted by this method.

When the density appears to be homogeneous, it is wise to take films of the chest with a Bucky diaphragm. By this means the varying

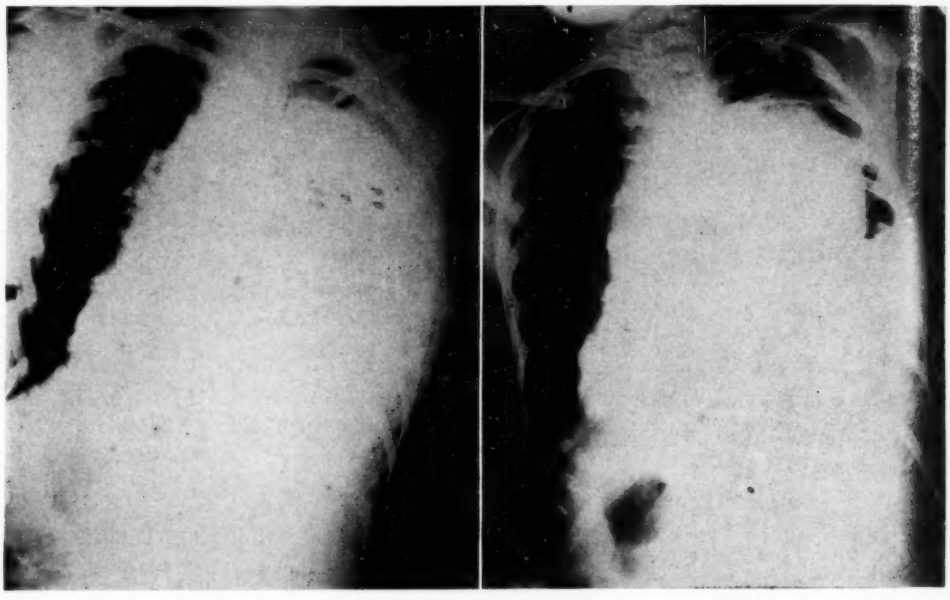

FIG. 3A FIG. 3B

FIG. 3A. Homogeneous density throughout right chest cavity; the cardiac shadow merges with the density; no definite diagnosis possible from film only.

FIG. 3B. After removal of 300 cc. of fluid, air (diagnostic pneumothorax) was reinjected. Note now the tumor mass, air and fluid level. Biopsy showed the tumor to be Hodgkin's disease.

densities can be noted and sometimes the original tumor can be made out. Another most important consideration is the state of the ribs and also the spine. Rarefactions can easily be noted on the film taken with the Bucky diaphragm. These rarefactions are usually due to metastatic lesions and of course suggest the futility of attempting surgery.

Of recent development in roentgen ray technique is the planigraph or tomograph. With this apparatus, which at first sight seems complicated, it is now possible to take films showing lesions at different depths

of the lung and obscuring the rest of the organ. This is accomplished by certain focusing devices which enable the beam of the roentgen ray to remain at a given level while the film moves in an opposite direction.

It does take a large experience to appreciate the finer differences noted in the film, but it has been shown that our roentgenological findings and autopsy reports have been almost identical, since the newer methods of roentgenological diagnosis have been developed.

FUNGUS INFECTION

The various fungi produce lesions more or less similar in character. The infection usually shows signs similar to tuberculosis or bronchopneumonia. As there is no definite picture associated with the various fungi, one can say that, when the lesions and the clinical history are not correlated, sputum studies should be carefully made. Not only should cultures be made but guinea-pig inoculations should be done.

CONCLUSIONS

The roentgen ray studies of nontuberculous lesions have shown the possibility of recognizing most pathological conditions.

It is important that the clinical history, physical signs and laboratory reports should be known before making a definite roentgenological diagnosis.

Newer techniques with the Bucky diaphragm kymograph and tomograph have been most helpful in advancing our diagnostic acumen.

BRONCHOSCOPY IN CHRONIC NONTUBERCULOUS INFECTIONS OF THE LUNG[1]

PAUL C. SAMSON[2]

Bronchoscopy rapidly is assuming its just position as an important procedure in the diagnosis and treatment of many chronic nontuberculous bronchial and pulmonary infections. These include bronchiectasis, pulmonary abscess, chronic suppurative pneumonitis and the various types of chronic bronchitis.

For bronchoscopy to be of the greatest value, the operator must be able to perform an examination which is technically adequate and have a thorough knowledge of pulmonary disease. It is most important that the bronchoscopist be a consultant as well as a technician. Since the number of medical and surgical thoracic specialists is increasing, it is probable that these men will do the bulk of the bronchoscopic work in the future.

It is to be emphasized that bronchoscopy never should be used as the sole procedure either diagnostically or therapeutically. From a diagnostic standpoint the operator should have a knowledge of the history, physical and laboratory findings and should have studied the thoracic roentgenograms. Therapeutically, bronchoscopy should be combined with measures which will aid in general hygienic betterment. These include strict bed-rest in some cases; postural drainage at frequent intervals; high-caloric high-vitamin diet with reduced iron; graduated heliotherapy; elimination of foci of infection in the teeth, tonsils, sinuses; a course of neoarsphenamine in fusospirochaetal infections. In selected patients, autogenous vaccines may be employed, but their routine use does not seem to be justified. In some clinics a temporary paralysis of the diaphragm occasionally is produced to increase pulmonary rest.

Clinically, a diagnosis of "chronic" may at times be difficult to make in bronchopulmonary lesions. The pathological criteria of chronicity are increased fibroblastic proliferation, the formation of mature scar tis-

[1] Read as part of the Symposium on *Chronic Nontuberculous Infections of the Lung* at the joint session of the Pathological and Clinical Sections at the 34th annual meeting of the National Tuberculosis Association, Los Angeles, California, June 21, 1938.

[2] 411 Thirtieth Street, Oakland, California.

sue and the predominance of round cell infiltration over polymorphonuclear invasion. These changes usually occur as early as six weeks from the time of onset of acute pulmonary symptoms. For this reason we have arbitrarily chosen from six to eight weeks as the time at which pulmonary lesions may become chronic.

Purulent foci in the body require adequate drainage and this is of utmost importance in bronchopulmonary suppuration. As long as the bronchial drainage remains sufficient, radical surgery may be postponed. Adequate drainage often is prevented either by localized or diffuse obstruction in the bronchi leading to the infected area in the lung. If the obstruction is localized its nature can best be determined by bronchoscopic examination. The most frequent causes are nonopaque foreign bodies, neoplasms, either benign or malignant, chronic inflammatory granulomata, ulcerated calcareous lymph nodes, endobronchial fibrostenosis and compression stenosis from an extrinsic neoplasm, abscess or aneurysm. Often, local treatment can be instituted immediately through the bronchoscope. Foreign bodies and obstructing tissue may be removed with forceps and fibrostenoses may be dilated. Recently, specially designed high-frequency cautery electrodes[3] have been used in the destruction of obstructive flattened granulomata and neoplasms which could not be removed entirely by forceps. Only a few cases have been treated in this manner but the results seem to justify the inclusion of these cautery instruments in the armamentarium of the bronchoscopist. Measures of this type usually cause an effective increase in drainage. As a rule, the compression stenosis group cannot be treated bronchoscopically but an endoscopic examination will be of aid in the diagnosis of these conditions.

Chronic pulmonary infection often causes a diffuse inflammatory congestion and oedema of the bronchial mucosa and submucosa. This is due in part to increased inflammatory lymph drainage and in part to the local irritating action of purulent sputum on the mucosa. The result is a very effective diffuse obstruction to drainage, particularly in the smaller bronchi and bronchioles (figures 2A and 2B). Treatment of the inflamed mucosa with bland oils and medicaments usually is of little value because the mucosal changes are secondary to pulmonary infection. In contrast, the bronchoscopic shrinkage of the mucosa is of great value in improving drainage. Our preference is for a solution

[3] These instruments were made for the author by Mr. George Becker, MultiArc Laboratories, 4026 Grove Street, Oakland, California.

composed of equal parts of ten per cent cocaine and five per cent ephedrine. The solution is applied topically with an applicator and effectively introduced into the smaller bronchi during deep inspiration with a bronchoscopic atomizer of the Clerf type. In favorable cases the effects of mucosal shrinkage last for from seven to ten days and improvement in the appearance of the mucosa can be seen readily at the time of succeeding bronchoscopies. Shrinkage is, of course, combined with the thorough aspiration of tenacious purulent sputum which by itself may cause partial obstruction to the lobar and tertiary bronchi (figures 1A and 1B). Bronchoscopy is of further value in eliciting the so called "selective cough," which has been stressed by Tucker (1), Jackson (2) and others.

In general, the older the pulmonary infection, the less well it responds to conservative treatment. Following bronchoscopy, improvement may occur sufficiently to decrease the risk of subsequent radical surgery. This is particularly true if there has been an acute exacerbation of a chronic infection. The value of a series of bronchoscopic aspirations in selected cases is undoubted. A definite program of aspirations should be planned so that a series of three, four or five bronchoscopies are performed at from seven- to ten-day intervals. Unless there has been unquestioned clinical *and* roentgenological improvement during this time we feel that the performance of further endoscopies is, with rare exceptions, unwarranted.

There are few absolute contraindications to a well performed bronchoscopy. Recent myocardial infarction, cerebrovascular accidents, aortic aneurysms which are producing symptoms, and extensive laryngeal disease may be considered as contraindications. Haemorrhage is a contraindication only when there is evidence of active pulmonary destruction. If this is not the case, bronchoscopy during haemorrhage may give valuable information as to the source of the haemoptysis. Hypertension and even mild congestive cardiac failure are not absolute contraindications if there is need for a bronchoscopy.

CHRONIC PULMONARY ABSCESS

Attempts at cure in patients with chronic pulmonary abscess still leave much to be desired. It has been estimated that from 20 to 25 per cent of patients with pulmonary abscess become well spontaneously. In the remaining group the mortality still is appallingly high, with the

rates running from 30 to 40 per cent in many series. In part, at least, this high mortality comes from the sharp segregation of cases into medical and surgical groups, the too infrequent early use of the bronchoscope as a therapeutic procedure and undue delay in performing external drainage when more conservative means of treatment are unavailing. Bronchoscopy should be one of the earliest therapeutic procedures used. It has been stated that many of these patients are too sick to be subjected to bronchoscopy. Rather it should be said that they are too ill *not* to be bronchoscoped.

There should be greater appreciation of the fact that pulmonary abscess is an extremely unpredictable disease and that indications for a change in treatment may arise within two or three days. For this reason the therapy never should be considered either as strictly medical or strictly surgical. There should be early consultation between the internist and his thoracic surgery consultant so that the optimum time for changes in treatment can be decided upon without delay.

The bronchoscopic picture in uncomplicated abscess is that of intensely red inflammation of the stem bronchus on the affected side, often associated with more or less tracheitis. In rare instances there is localized superficial ulceration of the mucosa covered with obstructing granulation tissue. At times there is a polypoid hyperplasia of the mucosa which grossly may resemble a neoplasm. It is uncommon to see an actual membrane although there may be a coating of tenacious purulent sputum. In most instances the mucosa is granular and oozes readily on slight trauma. There is an associated oedema which is most marked surrounding the lobar orifice draining the cavity. The combination of mucosal oedema and plugs of partially inspissated pus often causes visible obstruction (figure 1A). In such cases shrinkage of the mucosa aids in the loosening and expelling of obstructing secretions. Where anatomically possible, the passage of long curved aspirators directly into the abscess cavity may be of assistance in improving drainage.

In chronic pulmonary abscess bronchoscopy often produces surprizing results but repeated aspirations should not be undertaken unless there is almost immediate clinical and roentgenological improvement. Usually such improvement will be manifest within a week after the first bronchoscopy.

The two cases reported below represent undoubted examples of cure by the addition of bronchoscopy to the plan of treatment.

FIG. 1A

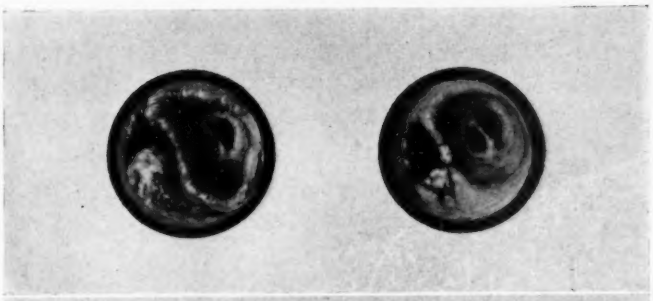

FIG. 1B

FIG. 2A

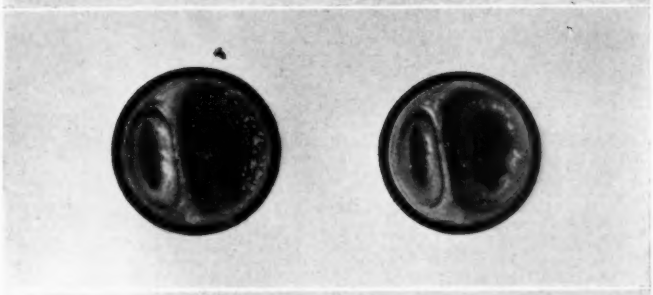

FIG. 2B

FIG. 3A

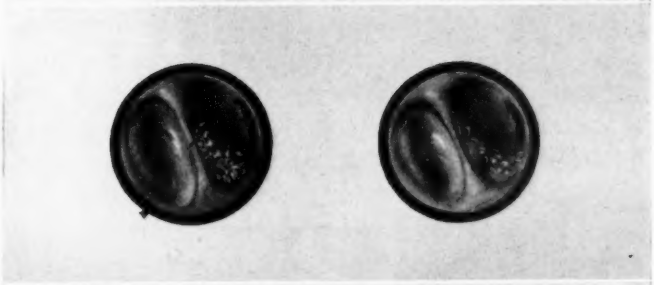

FIG. 3B

FIG. 4A

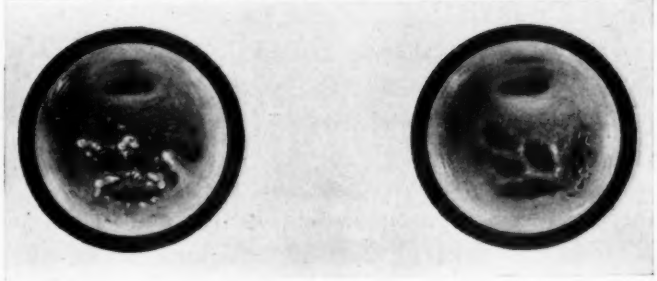

FIG. 4B

FIGS. 1–4

Case 1: C. W., a white male, age 71, was referred by Dr. Ergo Majors of Oakland shortly after he first saw the patient. The patient's health had been poor for one year. There was a three months' history of severe illness characterized at the onset by left-sided pleurisy, temperature of 102°–103°F. and racking cough with difficulty in raising from 200 to 300 cc. of foul sputum in 24 hours. The patient had been strictly confined to bed for three months and was slightly improved clinically, but the roentgenograms showed no essential improvement over those taken previously. The roentgenographic report by Dr. Joseph Coate was as follows: "The left upper lobe contains a large multilocular abscess cavity, showing several fluid levels." When seen by the writer the patient had lost 40 pounds in weight. He had a fever of 101°F. and was raising from 150 to 200 cc. of moderately foul purulent sputum in 24 hours. The white blood count was 20,350 and the haemoglobin was 68 per cent (Sahli). Bronchoscopy was performed at once and repeated six days later (figure 1). Within four days after the first bronchoscopy the sputum became odorless and the temperature normal. Four days following the second bronchoscopy all cough and expectoration ceased. Roentgenograms showed the abscess cavity to be greatly decreased in size. No fluid levels were visible. The patient convalesced rapidly. At bronchoscopy it was evident that partial obstruction was due predominantly to sticky purulent sputum. The cough had no force and secretions could not be efficiently dislodged. After aspiration and shrinkage much secretion was coughed from the upper lobar orifice. At the second examination the mucosa showed great improvement. A single globule of pus was aspirated from the left upper lobar orifice.

FIG. 1. Case 1. A: Bronchoscopic view of left upper lobar orifice. The partial obstruction is predominantly due to tenacious purulent sputum. Mucosal oedema is also present. B: Six days later. The mucosal oedema and congestion have subsided. A single globule of pus remains.

FIG. 2. Case 2. A: Full-lumen bronchoscopic view of right upper lobar orifice. The extensive mucosal swelling and granulation is causing sufficient partial obstruction to interfere with adequate drainage. Such mucosal change always extends into the smaller bronchi. B: Improvement in bronchoscopic appearance two weeks later. Slight congestion and oedema persist, but the orifice is larger and pus can now be expelled freely with cough.

FIG. 3. Case 4. A: Bronchoscopic view at the carina showing a localized area of polypoid mucosa on the mesial wall of the right stem bronchus, opposite the right upper lobar orifice. B: Two weeks later. Improvement in the bronchoscopic appearance paralleling the clinical progress. The areas from which the biopsy specimens were taken are shown.

FIG. 4. Case 5. Bronchoscopic notes: A: Just lateral to the middle lobar orifice, between it and the dorsal bronchus, is a sessile reddish firm mass, 3 mm. in length, which has persisted since the first bronchoscopy three months ago. It is surrounded by oedematous mucosa and appears to be a granuloma. The granuloma and the oedematous mucosa are cauterized carefully with the special high-frequency electrode, using the flattened ball-tip. B: One month later. Submucosal scarring visible in region of previous cautery. Granuloma entirely destroyed. Slight decrease in mucosal oedema of right lower lobe bronchus.

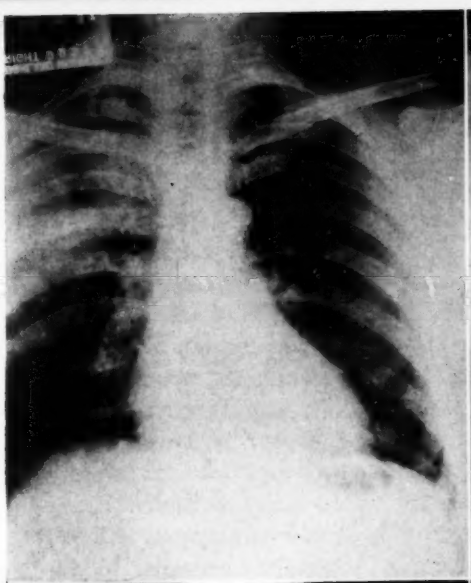

FIG. 5A

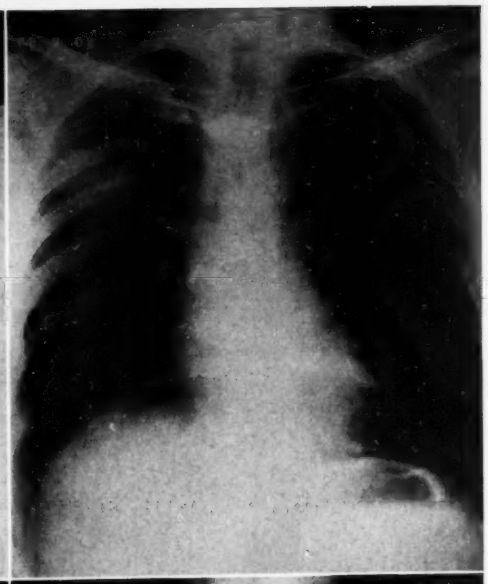

FIG. 5B

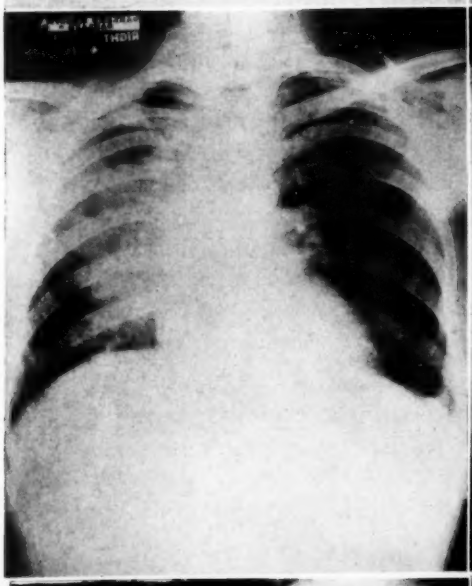

FIG. 6A

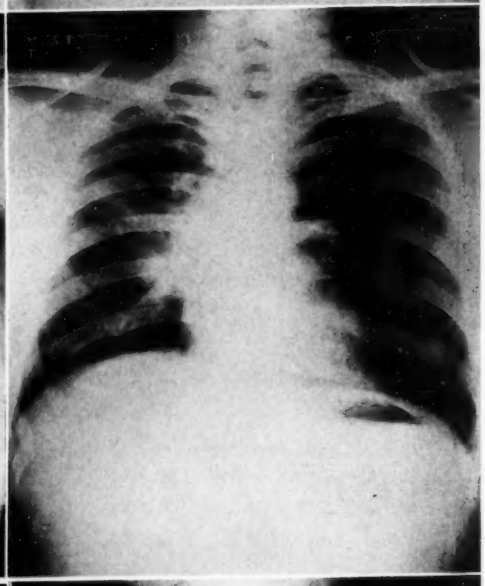

FIG. 6B

FIG. 7

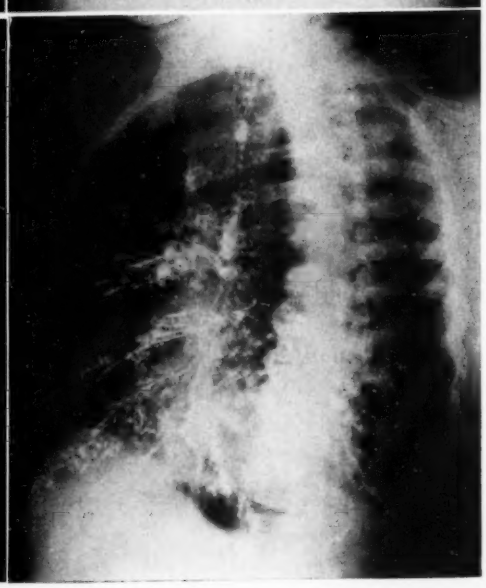

FIG. 8

FIGS. 5–8

Case 2: M. C., a 49 year old Portuguese male, was referred from the medical chest service of Dr. Harold Trimble at Fairmont Hospital, Oakland. The chief complaints were pain in the chest, cough, foul expectoration (300 to 400 cc. daily), low-grade fever and loss of weight. The patient had been ill for three weeks prior to his entry into the hospital. During the first month of his hospital stay, the patient was on a strict medical regimen, including absolute bedrest, postural drainages at frequent intervals and intravenous neoarsphenamine. There was no change in his symptoms and no improvement roentgenologically (figure 5A). Bronchoscopy was then added to the above regimen and a series of five performed at two-week intervals. There was then immediate improvement both clinically and roentgenologically (figure 5B). Within four days after the first bronchoscopy the sputum was averaging less than 150 cc. in 24 hours. At the present time the patient is well. A recent fluoroscopy revealed a few fibrous strands in the right upper lobe. At the first endoscopic examination the mucosa of the right upper lobar bronchus was markedly oedematous and granular (figure 2A). There was sufficient obstruction at and beyond the orifice so that pus trickled from the ostium. Succeeding bronchoscopies showed the oedema and granularity to be progressively lessening. Pus was expelled freely from the orifice with coughing.

In some patients the response to bronchoscopy is not sufficiently favorable for a cure to be expected. In many of these, however, there is much improvement and external drainage may be undertaken with greater safety. This is well illustrated in the following case.

Case 3: T. W., a Chinese male of 40 years of age, was referred by Dr. John Lagan of San Francisco shortly after having been seen by him. The present illness of approximately eight weeks' duration was characterized by productive

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FIG. 5. Case 2. A: Posteroanterior roentgenogram showing large multilocular cavity with surrounding pneumonitis in right upper lobe. There had been no roentgenological change after five weeks on strict medical care. B: Roentgenogram taken two days following the second bronchoscopy and sixteen days following A. The cavity has greatly decreased in diameter and the surrounding pneumonitis is almost gone.

FIG. 6. Case 4. A: Posteroanterior roentgenogram showing a diffuse mottled infiltration of the right upper lobe. B: Roentgenogram taken one week following the second bronchoscopy and one month following A. There is considerable clearing. Hilar infiltration persists.

FIG. 7. Case 5. Bronchogram in right lateral projection showing saccular bronchiectasis in the right lower and middle lobes.

FIG. 8. Case 7. Bronchogram in left anterior oblique projection. The unquestioned bronchiectasis in the left lower lobe has been superimposed upon the spine. There is good filling of the right bronchial tree and no bronchiectasis is seen. Bronchoscopically there was much purulent sputum coming from the right lower lobe, and it must, therefore, be called a chronic purulent bronchitis.

cough with extremely foul sputum, loss of weight and increasing fever. The patient was raising from 500 to 600 cc. of sputum in 24 hours. At the time of examination the patient was extremely toxic, was coughing almost constantly and had a fever of 104°F. The white blood count was 32,500. Roentgenograms showed an abscess nearly filled with debris, situated in the right middle lobe. Bronchoscopy was performed on two occasions, seven days apart. The cavity in the middle lobe was aspirated directly and the oedematous mucosa shrunken. There was great clinical improvement. The cough was less, the fever dropped to 100°F., and the white blood count fell to 14,400. Roentgenograms showed that the cavity now was draining more thoroughly, but it did not decrease in size. The initial response to bronchoscopy was good but there was no evidence of healing by roentgenogram and it was felt that further aspirations were not warranted. The patient was closely observed for two weeks following the second bronchoscopy. He continued to raise approximately 400 cc. of sputum in 24 hours, the white blood count increased to 22,500 and roentgenograms showed a gradual filling of the abscess. External drainage was, therefore, instituted three weeks after the original bronchoscopy. The patient is well.

In chronic pulmonary abscess the chief contraindication to bronchoscopy is massive haemorrhage which means destruction of pulmonary tissue. Bronchoscopy often aggravates the haemorrhage with bad results. In gangrene of the lung, bronchoscopy can be expected to accomplish little. Its use is chiefly diagnostic, and external drainage should be planned as soon as possible.

CHRONIC SUPPURATIVE PNEUMONITIS

The problem here is essentially the same as with pulmonary abscess as far as the bronchoscopic aspects are concerned. Mucosal oedema, granulation and congestion may be present. Occasionally the mucosa may assume a hyperplastic or even neoplastic appearance because of inflammatory change (figures 3A and 3B). Operation, usually lobectomy, should be considered if bronchoscopic aspiration and the usual supportive regimen outlined earlier fail of cure.

Case 4: L. E. was a 36 year old Mexican male, referred from the medical chest service of Dr. Harold Trimble at Fairmont Hospital. The patient had been ill approximately for ten weeks with productive cough, fever, loss of weight and recent haemoptyses. There had been no improvement with one month's bedrest at home. The probable diagnosis was suppurative pneumonitis following a lobar pneumonia which had failed to clear. Two bronchoscopies caused sufficient improvement in drainage to afford nearly complete resolution of the

right upper lobe lesion (figures 6A and 6B). Unfortunately it has been impossible to obtain a recent follow-up on this patient. When last seen, four months after discharge, he felt well. There was a slight residual cough productive of from 5 to 10 cc. of mucoid sputum. Marked hilar infiltration persisted on fluoroscopic examination. The condition of the bronchial mucosa was of particular interest in this patient. It illustrated the bizarre picture that may be associated with inflammation and the rapidity with which secondary mucosal changes may improve as the pulmonary condition becomes better.

The bronchoscopic notes were, in part, as follows. First examination: On the right, quantities of purulent secretions were coming from the upper lobe and the orifice was well visualized; on the mesial wall of the stem bronchus opposite the upper lobar orifice, the mucosa bled easily, was greatly thickened and apparently hyperplastic. It was possible that this was granulation tissue, but there was no visible ulceration and no membrane. It was not typically neoplastic but was sufficiently suggestive for a specimen to be taken for microscopical examination (figure 3A). Second examination (two weeks later): Diffuse mucosal congestion on the right, with localized ease of bleeding. The area from which the biopsy specimens were procured was definitely improved. Hyperplasia and oedema were diminished (figure 3B). Mucopurulent secretions in small amounts still came from the right upper lobe. The pathological report was made by Dr. Gertrude Moore: "Polypoid bronchial mucous membrane showing chronic inflammation."

It seems probable that the continuous irritating action of purulent sputum expelled from the lobar bronchus against the opposite wall of the stem bronchus was sufficient to cause this polypoid inflammatory response of the mucosa.

CHRONIC BRONCHIECTASIS

In bronchiectasis, bronchoscopy usually reveals diffuse dull red mucosal inflammation. There is moderate granulation and ease of bleeding, becoming more marked as the pathological lobe is approached. Succeeding bronchoscopies may demonstrate improvement in the appearance of the mucosa. Nonspecific inflammatory granulomata may be seen. These may be destroyed by careful cauterization.

Case 5: M. C. was a 20 year old white female referred from the medical chest clinic of Dr. Elliott Smart at San Joaquin General Hospital, Stockton, California. She had had productive cough, purulent sputum and occasional haemoptyses for many years. Bronchograms revealed bronchiectasis of the right lower and middle lobes (figure 7). The improvement following a series of four bronchoscopies was not sufficient and lobectomy now is being considered.[4] This

[4] The first stage of a "delayed" two-stage right lower and middle lobe lobectomy was performed on August 22, 1938, without incident.

patient had a small granuloma which persisted. At the time of the third bronchoscopy it was carefully cauterized with the high-frequency electrode, using a ball-tip. One month later, the granuloma had completely disappeared (figures 4A and 4B).

A cure of the pathology in bronchiectasis cannot be expected except by operative removal of the diseased pulmonary tissue. Since, however, lobectomy and pneumonectomy still carry a considerable risk, one is justified in attempting an amelioration of symptoms by bronchoscopy. Cough and sputum may completely disappear for several years following a series of bronchoscopic aspirations. The following case illustrates this point.

Case 6: A. Y., a white female, aged 32 years, was referred from the Medical Service of the University of Michigan Hospital, Ann Arbor, Michigan. Three months before admission and following the removal of teeth, she developed pain in the left chest, productive cough and had haemoptyses. There was a loss of weight of ten pounds and the patient suffered drenching night sweats. On admission she was running a fever of from 100° to 101°F. and was raising from 70 to 100 cc. of purulent sputum in 24 hours. The white blood count was 13,600. Lipiodol bronchograms showed saccular bronchiectases of the left lower lobe and lingula of the left upper lobe with surrounding pneumonitis. Three bronchoscopies at weekly intervals were performed, followed by a temporary paralysis of the left diaphragm. The first bronchoscopy revealed granulation tissue in the right stem bronchus and purulent secretions on this side. Subsequent examinations showed complete disappearance of the granulation tissue and of the purulent secretions on the right. On discharge from the hospital, thoracic roentgenograms showed little change. Clinically, however, the patient rapidly returned to complete health for two and one-half years. There was no cough or sputum and the original weight was regained. Recently she has had a repetition of the haemoptyses and for this reason lobectomy is now being considered.

In bronchiectasis, an associated contralateral bronchitis may give rise to relatively large amounts of purulent sputum. This will not be demonstrated by a bronchogram and bronchoscopy is the sole means of determining its presence or absence (case 7). When operation is being considered it is important to know that sputum may be coming from the opposite side. Contralateral bronchitides of this type may become entirely quiescent following several bronchoscopic aspirations.

There are many patients on whom radical surgery for bronchiectasis

is unwise because of bi- or tri-lobar infection, age or extrapulmonary disease. In such individuals the aim of treatment is symptomatic improvement of troublesome cough and expectoration. When such relief can be obtained there is every justification for performing bronchoscopic aspirations indefinitely at from one- to three-month intervals. Improvement lasts for an increased length of time following the first series of weekly aspirations and the majority of patients will return voluntarily for treatment when cough and sputum again become annoying. Obviously, postural drainage should be insisted upon between bronchoscopies. It is to be emphasized that bronchoscopy becomes entirely incidental to these patients. They require no hospitalization and many can be treated with little local anaesthetic. Discomfort either during or following bronchoscopy is minimal.

Case 7: A. J. was a 57 year old white male, referred from the Medical Chest Service of Dr. Harold Trimble at Fairmont Hospital, Oakland. A year prior to study there had been an insidious onset of productive cough, slight loss of weight and weakness. The patient raised from 150 to 175 cc. of green tenacious purulent sputum in 24 hours, which had a musty odor. He had exhausting spasms of coughing. Often he was awakened at night by coughing. Bronchograms (figure 8) showed bronchiectasis in the left lower lobe but the right bronchial tree appeared to be normal. All bronchoscopies have shown, however, that at least 25 per cent of the purulent sputum is coming from the right lower lobe. These secretions definitely are not of the spill-over type since they persistently come from the tertiary branches of the right lower lobe after all secretions in the stem bronchus have been aspirated. The mucosa at the right base is congested. In all, four bronchoscopies have been performed. The patient feels that he is greatly improved. He now expectorates approximately 60 cc. of odorless sputum in 24 hours. There are no spasms of coughing and the patient is no longer awakened at night. Since the operative risk in this patient is excessive, bronchoscopies will be continued as long as there is improvement.

CHRONIC BRONCHITIS

This term includes a heterogeneous group of bronchial infections in patients whose chief complaint is an irritating productive cough. Thoracic roentgenograms, both with and without lipiodol, often fail to reveal sufficient pathology to account for the symptoms. Various descriptive terms have been used, depending somewhat upon the type of sputum raised and upon the toxicity exhibited. These include chronic

suppurative bronchitis, chronic suppurative bronchiolitis, chronic putrid bronchitis, chronic fibrinous bronchitis.

Bronchoscopically one may find localized bronchial obstruction and a secondary bronchitis distally because of stagnation of secretions. The process, however, may be generalized in one or both bronchial stems apparently from a primary bronchial infection which has persisted. The forced hacking cough is particularly distressing in diffuse obstructive infections such as fibrinous bronchitis or bronchiolitis. Aspiration of sputum, removal of casts and shrinkage of inflamed mucosa give dramatic relief. The decrease in cough and even cessation of expectoration are a great source of satisfaction both to the patient and to his physician.

In selected cases the use of bland oils and substances such as mono-p-chlorophenol may be used through the bronchoscope.

Chronic "asthmatic" or asthmatoid bronchitis is a condition in which the aetiology is not always clear. The clinical syndrome is fairly definite and usually appears during the fifth and sixth decades of life. It is characterized by distressing productive cough, persistent wheezing, progressive dyspnoea and increasingly frequent periods of cyanosis usually accompanying the attacks of coughing. The sputum is extremely tenacious, sometimes frothy but is only moderately purulent. It is difficult to raise and the cough is not efficient. Cardiac function usually is adequate. Many of these patients have a past history of severe hay fever, but when seen in the condition described above, allergy appears to be no longer a factor, having been "burned out" as it were. Desensitization does not aid these individuals. The usual roentgenographic findings are emphysema and increased bronchovascular markings. An old pleuritis or slight degree of bronchiectasis may be associated. These individuals have a respiratory decompensation.

Bronchoscopy may offer great relief in this condition. There is diffuse bilateral bronchial congestion. Small plugs and strings of tenacious mucopurulent secretion partially block all lobar and visible tertiary bronchi. Obviously such obstruction extends well beyond the region visualized by the bronchoscope. Air exchange increased by dyspnoea over a period of many days may cause drying of the secretions, and forceps removal of inspissated plugs at times may be necessary. The treatment of choice consists of careful and complete aspiration of all obstructing material together with thorough shrinkage of the mucosa.

Recently, irrigation with hypertonic Bledsoe-Fisher solution has been employed with success as a further step. Inspection of the irrigating fluid after aspiration has shown that it contains numerous fine mucopurulent flakes and filaments, some of the latter in the form of casts. Undoubtedly this is a manifestation of bronchiolar obstruction. The action of irrigation in the loosening and extrusion of these tenacious masses is very beneficial. Minter (3) has described the supraglottic administration of Bledsoe-Fisher solution in the treatment of chronic bronchiectasis. Patients with emphysema and asthmatoid bronchitis, however, have a vital reserve which is greatly lowered. It has, therefore, seemed much safer to perform irrigations through the bronchoscope, sharply limited to one lobe or one lung at a time. From 20 to 30 cc. of the solution are injected, the patient is instructed to breathe rather deeply without coughing, if possible, for from ten to fifteen seconds. All of this solution is then aspirated before there is any further injection. Dr. Karl Deissler of Oakland has made the valuable suggestion that epinephrine be added to the irrigating solution to aid in overcoming any possible bronchial spasm which might result from the use of a slightly hypertonic solution. In general, irrigation through the bronchoscope gives much better control of the suffocative factor and immediate aspiration can be undertaken when necessary.

The patients should understand that this treatment is purely symptomatic and in no way corrects the underlying pathology. The majority, however, willingly undergo further bronchoscopies when the need arises because of the relief obtained.

SUMMARY AND CONCLUSIONS

The indications for bronchoscopy as a diagnostic and therapeutic procedure in chronic bronchopulmonary infections are described. The importance of adequate drainage is stressed. The rôle of localized and diffuse bronchial and bronchiolar obstruction is emphasized, with particular reference to the establishment and maintenance of bronchopulmonary suppuration.

Special problems may arise in connection with chronic pulmonary abscess, suppurative pneumonitis, bronchiectasis and chronic bronchitis. These are discussed in detail, using illustrative case reports.

In conclusion, every patient with any type of chronic bronchopulmonary suppuration should have the benefit of at least one bronchoscopy

as a diagnostic procedure. Many of these patients should receive the benefit of a series of therapeutic bronchoscopies before radical surgery finally is decided upon.

The author is grateful to the administrations of the following hospitals for their permission to use hospital records and to reproduce roentgenograms: University of Michigan Hospital, Ann Arbor, Michigan; Alameda County Institutions, Oakland; San Joaquin General Hospital, Stockton; Peralta Hospital, Oakland; The Chinese Hospital, San Francisco; St. Francis Hospital, San Francisco.

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SURGICAL TREATMENT OF NONTUBERCULOUS PULMONARY SUPPURATIONS[1,2]

HAROLD BRUNN AND ALFRED GOLDMAN

The presentation of all nontuberculous pulmonary suppurations would be too voluminous for this symposium. We have, therefore, chosen to discuss four clinical types. These are: first, putrid pulmonary abscess; second, bronchiectasis; third, suppuration associated with bronchial obstruction resulting from neoplasm; and fourth, a brief presentation of coccidioides, a case of which was recently operated at our clinic and is of considerable interest. For this discussion we shall present our own experiences rather than those found in the literature.

PUTRID PULMONARY ABSCESS

The treatment of putrid pulmonary abscess is still controversial. We believe each case to be an individual problem requiring early diagnosis, constant clinical and roentgenological observation, and, when indicated, early rather than late surgical drainage. A certain number of patients, 31 per cent of our first series (see table 1) and 24 per cent of our second series (see table 2), have improved spontaneously under medical regimens. We therefore prefer in general that acute abscesses have preliminary medical treatment for a limited time (two months) in order to avoid operating upon those patients who would become well without surgical drainage. On the other hand we condemn continuation of postural (1) or bronchoscopic drainage, pneumothorax, the new intravenous therapy of alcohol (2) and sodium benzoate (3), sanatorium regimen or other medical methods that may be suggested until the abscess becomes chronic. Our early statistics (4) showed that results following surgery

[1] Read by Dr. Alfred Goldman as part of the Symposium on *Chronic Nontuberculous Infections of the Lung* at the joint session of the Pathological and Clinical Sections at the 34th annual meeting of the National Tuberculosis Association, Los Angeles, California, June 21, 1938.

[2] From the Department of Surgery, Division of Thoracic Surgery, University of California Medical School, and the Department of Public Health, San Francisco Hospital, San Francisco, California.

[3] Supported by the Lillie Spreckels Wegeforth Fund.

were best when operation had been performed relatively early, within one hundred days. During the past three years a greater percentage of patients have been operated and these earlier in the course of the disease than in previous years. (Compare table 1 with table 2.)

We prefer the two-stage thoracotomy for drainage even though we suspect, after direct inspection, that the pleura is firmly adherent. Localization of the peripheral adherent area overlying the abscess is obtained by X-ray and bronchoscopic examination. The incision is planned

TABLE 1

Results of medical treatment of pulmonary abscess

First Series. Before May 1, 1934. Total number of cases 205

	TIME FROM ONSET UNTIL INSTITUTION OF MEDICAL OR OPERATIVE TREATMENT—AVERAGE DAYS
31% or 63 cases Improved	123
34% or 72 cases Operated	460
35% or 70 cases Died	186

TABLE 2

Results of medical treatment of pulmonary abscess

Second Series. May 1, 1935 to June 1, 1937. Total number of cases 45

	TIME FROM ONSET UNTIL INSTITUTION OF MEDICAL OR OPERATIVE TREATMENT—AVERAGE DAYS
24% or 11 cases Improved	330 (1 case 1680)
54% or 24 cases Operated*	212
22% or 10 cases Died	300 (1 case 730)

* 4 cases had successful artificial pneumothorax.

to approach the abscess in this area. When the abscess lies beneath the scapula we prefer a vertical axillary incision to a posterior paravertebral one. The first stage is performed under local anaesthesia but subsequent stages are done without anaesthesia. At the first stage two or three ribs overlying the abscess are freed subperiosteally but not resected. Vaseline gauze packing or gauze soaked in dilute iodine is inserted between these ribs so as to make slight pressure against the cavity. A lead bead is fixed on the parietal pleura as an X-ray marker, and the wound is closed with superficial drainage. The gauze pressure against the cavity will often ameliorate the symptoms very considerably and the

patient improves markedly. X-ray films are taken again to insure proper location and in seven to fourteen days the second stage is performed without anaesthesia. The old wound is reopened, ribs, drain and packings are removed; and through the pleurae now thoroughly adherent, the abscess is approached with the actual cautery. This is done slowly and carefully and the cavity is unroofed; the abscess is evacuated with suction and packed loosely with one-inch strips of moist gauze. Subsequent cauterizations are often necessary. Persistent bronchial fistulae are treated with muscle plastic closure (5, 6). Complicating bronchiectasis may require lobectomy.

The poorer results of late surgery (4) are related to the pathological changes associated with chronic abscesses. In some cases these changes appear early so that a small, soft, well circumscribed area of necrosis (7), localized to one bronchial segment, multiplies itself into several abscesses, which may in turn coalesce to form a larger single loculated abscess (figure 1, A to C). In others, firm fibrosis occurs early, preventing collapse of the excavation when the cavity is drained. Furthermore, air embolus, brain abscess and severe haemorrhage are complications which more frequently occur in late cases (4). Bronchial changes decrease the efficiency of the lung's natural drainage and bronchiectasis ensues (figure 2, A and B). These morphological changes are demonstrable by careful X-ray studies and by endobronchial probing with serial selective bronchography, fluoroscopically controlled (8) (figure 1, B1 to B3). Finally death may result from metastatic brain abscess, air embolus, sudden massive haemorrhage, flooding of the noninvolved lung with the contents of the abscess, or rupture of the abscess into the pleural cavity. During the past three years we think we have avoided these late disasters because we operate earlier and in two stages (see table 3).

Marked bronchiectatic changes as well as other features associated with chronic abscesses are well illustrated in the following case.

Case 1: G. M., female, age 27. First entry to University of California Hospital, June 28, 1933. Discharged July 20, 1933. Second entry September 29, 1933. Discharged November 20, 1933. Onset several days after confinement, with cough, sputum and pleurisy. During labor an inhalation anaesthesia was administered. A haemolytic streptococcal empyema was drained one month later, March, 1932. Cough, foul sputum and fever recurred intermittently after the empyema was healed. Eight months later, November, 1932,

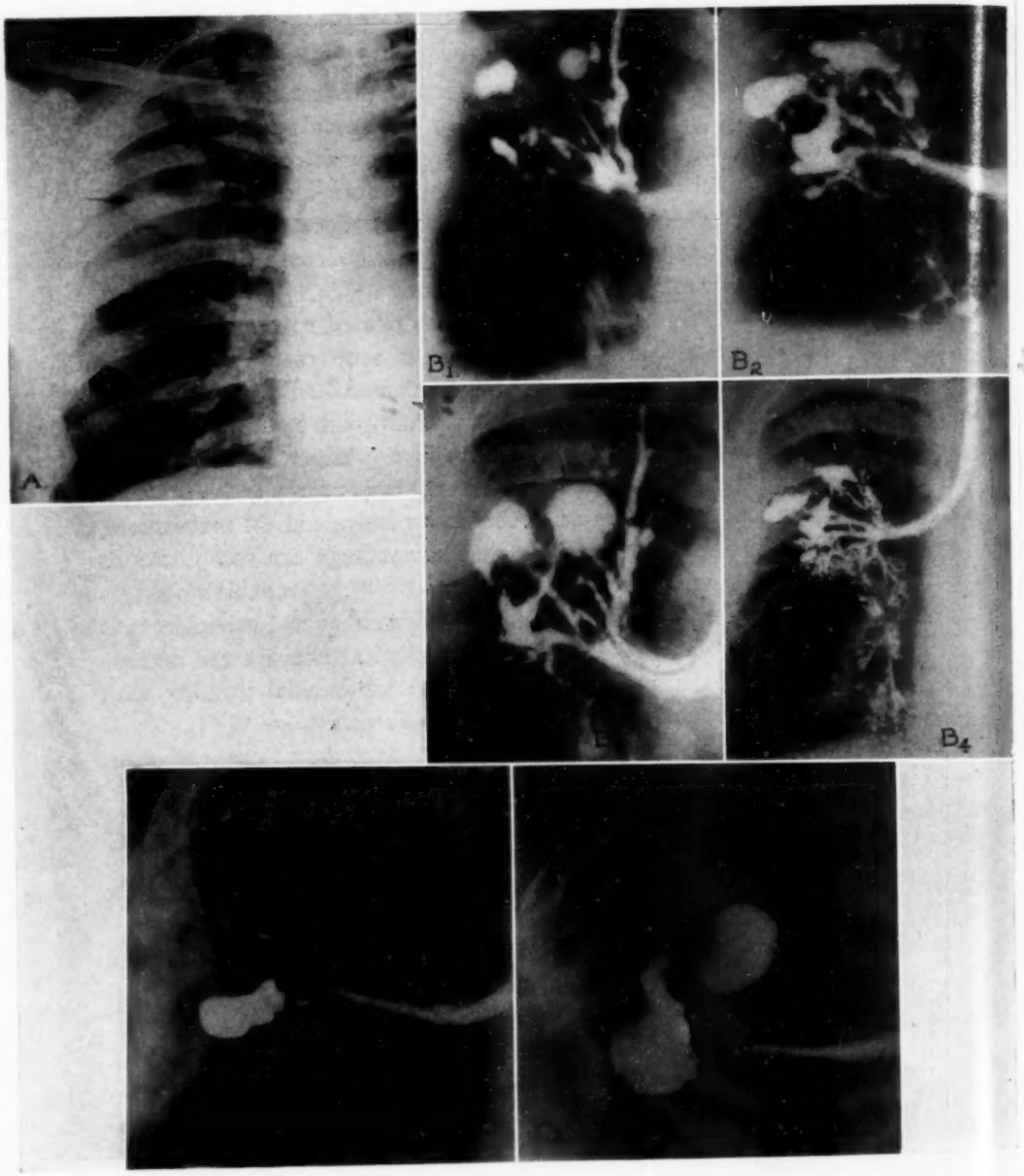

FIG. 1

the patient was expectorating one pint of foul sputum daily, and in February, 1933, X-ray films taken in a sanatorium showed an abscess cavity with a fluid level. Exploratory thoracocentesis there in March, 1933, resulted in air embolus from which she revived, but she continued downhill with dyspnoea, cyanosis and three to four cups of foul sputum daily. She entered the Uni-

TABLE 3

Results of surgical treatment of pulmonary abscess—comparison of first and second series†

First Series. Before May 1, 1934. Total number of cases 72

	TIME FROM ONSET UNTIL OPERATION—AVERAGE DAYS
55% or 40 cases Improved	410
45% or 32 cases Died	504

Second Series. May 1, 1935 to June 1, 1937. Total number of cases 24

	AVERAGE DAYS
79% or 19* cases Improved	201
21% or 5 cases Died	231

* 4 cases had successful artificial pneumothorax

† Preliminary medical treatment in all cases.

versity of California Hospital June 28, 1933, fifteen months after the appearance of foul sputum. On June 30, 1933, through an axillary incision, a large putrid abscess was evacuated. Several bronchial fistulae persisted and were

FIG. 1. Morphological changes depicted by endobronchial probing and serial selective bronchography (8) in a case of pulmonary abscess.

A: May 19, 1937. Six weeks after insidious onset. Single cavity with fluid level in right upper lobe. Acute abscess.

B: January 31, 1938. Serial selective bronchography "spot" films. "The abscess" is now nine months old and has reached the chronic stage.

B1: Prone position. Catheter in right upper lobe. Beginning filling: two cavities are shown above distorted bronchi.

B2: Further filling. Upright position. *Three* separate cavities with fluid levels are filled.

B3: Same as B2. Prone position. The fluid levels disappear and are replaced by three large globules. Cylindrically dilated bronchi around the multiple abscesses are filled.

B4: Six foot film of completed bronchogram. Catheter in right upper lobe. Upright position. Three fluid levels and surrounding bronchiectasis are well shown.

C: August 1, 1938. "The abscess" is now seventeen months old. Serial "spot films." Prone position. Catheter in right upper lobe. The three cavities have coalesced into one large cavity.

C1: Beginning filling of lower loculation of cavity.

C2: Both loculations contain large globules of lipiodol. By moving the patient about free communication between the two loculations was easily demonstrated.

present at discharge three and one half weeks later; but her symptoms had improved. Because of recurrent cough, sputum and fever, she reëntered the University of California Hospital, two months later, September 29, 1933. Multiple stage cautery lobectomy was performed because of several bronchiectatic abscesses in the right upper lobe. She was discharged November 20, 1933, with marked decrease of sputum. During the next two years there was steady clinical improvement despite residual bronchiectatic cavities in the

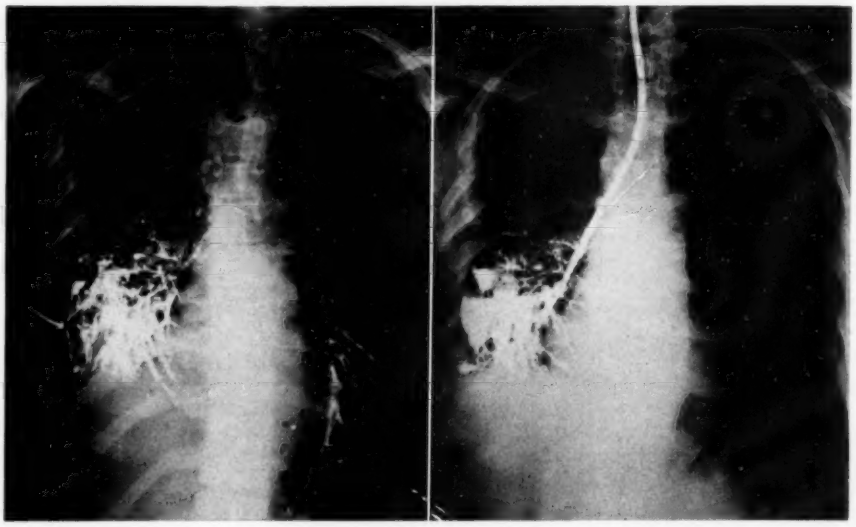

FIG. 2. Case 1. G.M. Occurrence of progressive bronchiectatic dilatations associated with "chronic abscess."

A: November 1, 1933. "Abscess" twenty-one months after onset (chronic) showing marked bronchiectasis and small fluid levels.

B: May 3, 1934. "Abscess" twenty-seven months after onset. Symptoms minimal but bronchial changes have progressed giving rise to several longer fluid levels and filled dilatations not present before.

lower lung which increased in size (figure 2B). She had no cough nor expectoration, had gained fifty pounds and was doing her housework comfortably in 1935.

BRONCHIECTASIS

Our views of the various surgical operations for bronchiectasis have been presented in a paper by Brunn (10), therefore we shall discuss only the lobectomy treatment of this disease. Bronchiectasis is now recognized to be a disease amenable to surgical removal by one-stage lobectomy. According to Bonniot and Monod (9) in the development of

lobectomy the phase of success belongs to the period of 1929 to 1936. They say *C'est la phase de succes: un nom et une date marquent son debut: Brunn, 1929* (10, 11, 12). During the next few years improvements in technique (Shenstone snare (13), Stephen's zipper-dam (14), and intratracheal anaesthesia) were made. However, O'Brien (15) writes in 1937, "To Brunn really belongs the credit for the present technique of our one-stage operation . . . his fundamental principles have not been changed." At this writing several hundred one-stage lobectomies for bronchiectasis have been performed in different clinics with a maximum mortality of 10 to 20 per cent, and a minimum of 3.5 per cent (Churchill (16)). A lower operative mortality is directly proportional to the type, state and extent of the disease; the greater number of lobes involved, the higher the mortality. The choice of case and the amount of lung to be resected are greatly aided when the extent, type and exact location of the bronchiectatic areas are known. Ordinary methods of bronchography often fail to distinguish the involvement in the various lobes. With endobronchial probing and serial selective bronchography fluoroscopically controlled (8) any accessible portion of a lobe may be selectively studied with lipiodol. By this technique, if lobectomy is considered, we now explore the lingula of the left upper lobe and the right middle lobe in all cases of suspected lower lobe involvement. When pneumonectomy is contemplated, the contralateral lung should be explored also, and if bilateral lobectomy is necessary, the lower part of the right upper lobe should likewise be explored.

In order to minimize the danger of empyema, several methods for producing adhesive pleuritis have been proposed (Alexander (17), Haight (18), Churchill (16), Bethune (19)). These proposals have led to the use of two-stage procedures, the indications (16) of which are still not well defined, nor has there been an accepted method evolved for the two-stage operation. In most thoracic clinics the one-stage operation is preferred. We prefer the one-stage procedure as originally set forth by Brunn (10, 11, 12), modified by the use of intratracheal anaesthesia, the mechanical bronchial snare, and the zipper-dam.

By means of a suitable intratracheal catheter, not only is an adequate airway maintained for proper anaesthesia, but by permitting frequent aspiration of bronchial secretion and purulent material expressed from the manipulated lung, postoperative spread is minimized. With the patient on the unaffected side, an intercostal Lilienthal incision is made between the seventh and eighth, or between the sixth and seventh ribs,

and developed down to the bony thorax. The posterior one inch of the two ribs above and below the proper interspace is resected before entering the pleural cavity in order to provide wider exposure and to avoid postoperative pain from overriding. Mobilization of the paravertebral muscles is done to aid in effecting an airtight closure. The pleural cavity is entered, care being taken to avoid cutting into the lung where it is adherent. Mobilization of the lung is carried out by severing adhesions about the lower lobe, particular care being taken with the pulmonary ligament which is always severed between clamps and tied. Fine adhesions may be cut without tying. Dense adhesions must be handled with great care in order to avoid entering the parenchyma of the lung and contaminating the field with virulent bacteria. Aside from freeing adhesions to the diaphragm and pericardium, dissections of the interlobar fissure may require careful cutting between clamps and tying, and even pleuralizing exposed parenchymal surfaces. Parietal or mediastinal adhesions to the upper lobe are never divided. It is often necessary to pause during this part of the operation while the anaesthetist sucks the bronchi clear of expressed secretions. When the lung has been freed on all sides up to the mediastinum, the zipper-dam is placed around the pedicle and the zipper drawn tight so that contamination of the thoracic wall and the pleural cavity will be minimal. The Shenstone snares (13) are placed around the pedicle and a cone shaped incision is made between them. Vessels and bronchi stand out as this is done, so that they are readily clamped and ligated. Bronchi are further trimmed down to the lobar bronchus which is carbolized and dissected deep within the stump before being tied. An airtight closure of the pedicle is made with two layers of running chromic sutures. The second layer approximates the pleural cuff so that the pedicle is thus pleuralized (11, 12). The remaining snare is loosened and further bleeding stopped before removing the snare and the zipper-dam. A rubber urethral catheter is inserted through the chest-wall below the incision to give dependent closed drainage of the pleural cavity. The pleural wound is closed by approximation of the ribs with three interrupted doubled chromic sutures and careful suturing of the paravertebral muscles over the posterior defect. The remainder of the wound is closed in layers. Before applying the dressings, the anaesthetist inflates the upper lobe and air is allowed to escape from the pleural cavity through the drainage tube, the tip of which is held under water. A routine transfusion of 500 cc. of whole blood is given immediately after opera-

tion. Secondary shock may occur several hours later, probably the result of exudation and absorption of the protein containing fluid in the pleural cavity. When this occurs a second transfusion is given. The pleural cavity is kept free of air and fluid by frequent aspiration. Permanent bronchial fistulae do not occur, but about the tenth to sixteenth day, when the pedicle sloughs, temporary bronchial fistulae occur, and associated with them may be two types of encapsulated empyema. One, around the pedicle, drains through the bronchus and is coughed up, the other along the lateral thoracic wall requires rib resection.

The following case illustrates the lobectomy treatment for bronchiectasis.

Case 2: J. B., white, male, age 15 years. Admitted to San Francisco Hospital on July 12, 1937; discharged September 20, 1937. He had cough and sputum for fifteen years. Since infancy patient had cough and sputum and at the age of one year so called pneumonia. As he grew older there was more sputum. Exercise, running and playing, brought on cough so that although he developed fairly well physically he became introverted and was unable to enjoy normal play or parties with other children. At the age of twelve he had bilateral radical antrum operations and at thirteen adenotonsillectomy. These procedures were followed by a regimen of postural drainage, intrabronchial codliver oil instillations and general measures. At fourteen years a left phrenic crushing was performed, six months before the present entry. With these measures a decrease from 150 to 60 cc. of purulent sputum occurred. However, there was no improvement in the morphology of his bronchial tree by bronchography nor did his mental symptoms change. Therefore he was admitted to the San Francisco Hospital for lobectomy.

Examination of the chest showed signs at both bases, more marked on the left. Fluoroscopy showed that the left diaphragm had partially recovered from the phrenic crushing. Previous X-ray films following lipiodol instillation showed marked club-shaped bronchiectases in the left lower lobe, lingula of the left upper lobe and moderate cylindrical dilatation in the right middle lobe. Laboratory work: haemoglobin 110 per cent or 16 gm., red cells 5.37 million, white cells 18,650, polymorphonuclears 82 per cent, lymphocytes 16 per cent; monocytes 2 per cent. Urine was normal. Sputum was 50 cc. daily, purulent and not foul. Cultures and colony counts showed alpha-streptococcus 50 per cent, *M. catarrhalis* 15 per cent; *Staphylococcus aureus haemolyticus* 10 per cent, Pfeiffer's bacillus 15 per cent, and gamma-streptococcus 10 per cent. Anaerobic cultures contained gram negative threads, diphtheroid bacilli and streptococci. No acid-fast microörganisms were seen on smear. Kahn and Wassermann reactions were negative.

On July 23, 1937 under intratracheal nitrous-oxide anaesthesia with avertin,

a one-stage resection of the left lower lobe and lingula of the left upper lobe was performed, by Dr. Harold Brunn. A partially developed interlobar fissure set off the involved lingula of the left upper lobe (figure 3). Transfusion was given after operation. Following operation, continuous suction at a pressure of from −4 to −10 cm. of water was maintained through the closed drainage tube. The wound healed *per primam*. On the twelfth postoperative day a bronchial fistula could be demonstrated by irrigating the drainage tube. On the twenty-fifth day empyema developed along the lateral thoracic wall and this was drained by rib resection. It held about 8 ounces, and a bronchial fistula could

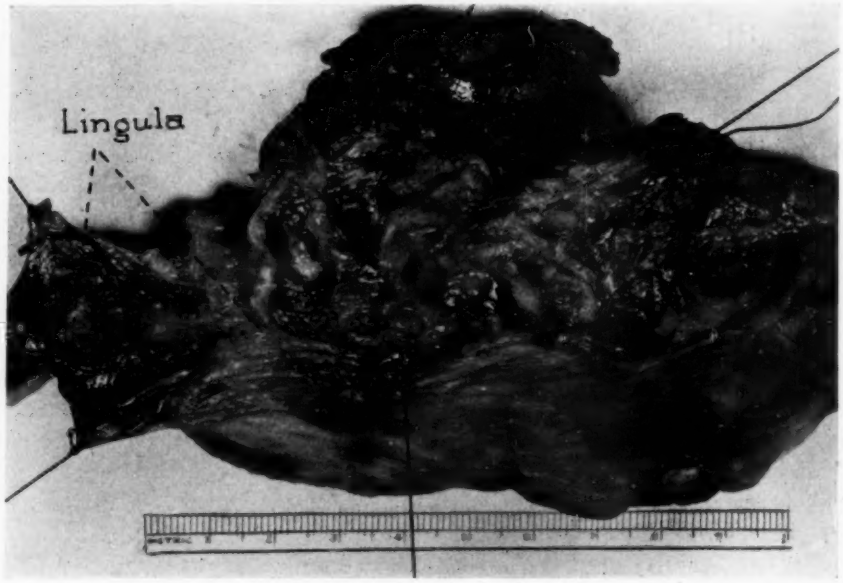

FIG. 3. Case 2. J.S. Lower lobe and lingula of left upper lobe. Lobectomy specimen removed by Dr. H. Brunn in one stage. Bronchiectatic bronchi are opened both in the lower lobe and in the lingula of the left upper lobe.

be heard in its depth. Five days later, on the thirty-third postoperative day, his temperature was again normal and remained so until his discharge on the fifty-eighth postoperative day. The empyema was entirely healed and the wound closed four months after lobectomy. He was last seen one year after lobectomy when he had gained ten pounds over his hospital weight, had 30 cc. of purulent sputum daily. Bronchoscopy disclosed purulent secretion coming from the left and right sides. Serial selective bronchography showed some short dilated bronchi about the stump on the left and moderate clubbed bronchiectasis in the right middle lobe.

Deep X-ray therapy for residual bronchiectasis as described by Berck (20) was tried after lobectomy with moderately effective results. We have used this method on a small number of cases with advantage in some but without effect in others.

NEOPLASTIC BRONCHIAL OBSTRUCTION

Pulmonary suppurations associated with bronchial obstruction from tumor occur when the tumor arises in the bronchus or grows into the bronchus from the outside or produces pressure causing occlusion of the bronchus. This subject has not received the attention it deserves. Death in these patients frequently results from the suppuration rather than from the neoplasm *per se*. Often the correct interpretation is not made until autopsy. Benign bronchial tumors are accompanied by parenchymal suppuration more frequently than malignant tumors. The cause of death in these cases is nearly always pulmonary suppuration. Bronchiectasis, interstitial pneumonitis, pulmonary abscess, empyema and metastatic infection are not uncommonly associated with such tumors. The term "drowned lung" is used to express a condition resulting from the damming up of secretions which can find no exit from the bronchial tubes (figure 4). That these secretions are under tension is well demonstrated by the gush of pus which occurs when the bronchus of a postmortem or surgical specimen is opened. This condition is clinically to be differentiated from pulmonary abscess (parenchymal necrosis). The former responds well to bronchoscopic drainage with removal of the bronchial block, the latter not at all.

The bacteria cultured usually are the ordinary pyogens, but not infrequently anaerobes from the buccal cavity, and higher bacteria such as streptothrix and leptothrix groups are present. Occasionally a pneumococcus is the cause of an infection which may appear to be a typical lobar pneumonia.

Removal through the bronchoscope is preferred when the tumor is benign, and can be totally removed in this way, thus permitting normal bronchial drainage. In order to cure irreversible bronchiectatic and parenchymal infection, lobectomy or pneumonectomy may be necessary even though the endobronchial obstruction can be bronchoscopically removed. Empyema and pulmonary abscess are treated by open thoracotomy. X-ray therapy is always dangerous when bronchial drainage of the infection is blocked by the tumor.

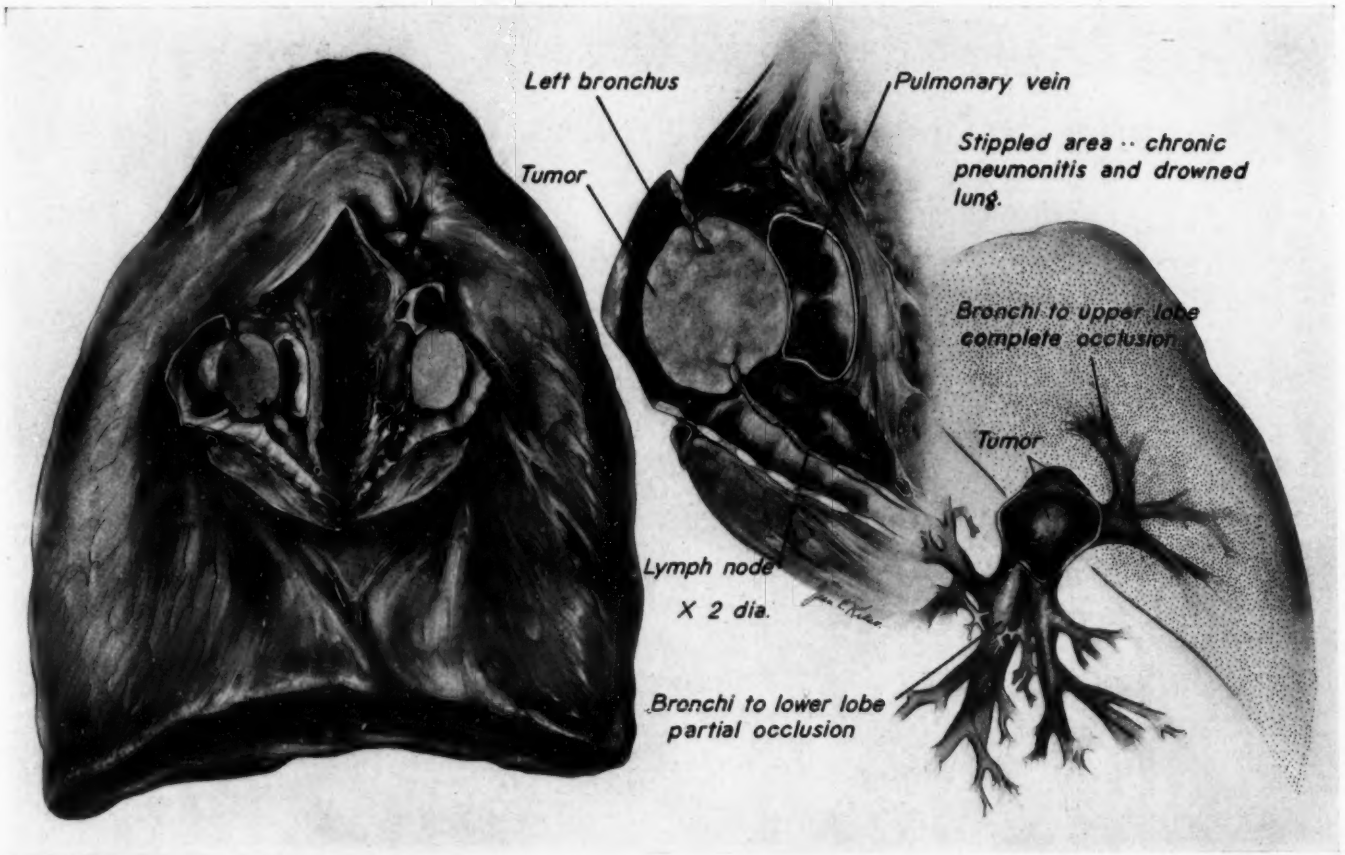

FIG. 4. Artist's drawing of total pneumonectomy specimen of left lung removed by Dr. H. Stephens. The stippled area designates the "drowned lung" caused by the bronchial block. Note that there is an extrabronchial portion of the "benign" tumor which could not have been removed through the bronchoscope.

The following case history illustrates not only the relief of symptoms afforded by endobronchial removal of benign tumors but also the bronchiectases they leave behind.

Case 3: E. D., white, male, age 17 at second entry. First entry to San Francisco Hospital June 21, 1935. Discharged July 3, 1935. Second entry May 2, 1938 and discharged June 24, 1938. Haemoptysis three and a half years ago. Cough and sputum for one week. The onset of the present illness was with haemoptysis three years before the second entry. This haemoptysis was bright red, sudden in onset and termination. Although it occurred on the way home from his father's funeral (his father died of pulmonary tuberculosis) it was preceded by a week of cough and sputum. His first entry to the San Francisco Hospital was four days later with fever, cough and sputum because of suspected tuberculosis, but sputum was negative for tubercle bacilli and contained pneumococci. Physical examination and X-ray films indicated an inflammatory process with partial atelectasis at the left base. He was discharged with a diagnosis of suspected tuberculosis July 3, 1935.

During the next three years he was fairly well, attending school regularly, but had frequent "colds" and he often came home "choked up" and wheezing. Four months before the second entry he had another haemoptysis of four ounces. Three weeks before the second entry he had a "cold," was in bed two weeks. Then after playing basketball he suddenly coughed up a tablespoonful of purulent sputum, began to vomit, fifteen times the first day. Five days later, the day before entry, he had a chill which was followed by fever and pain in the left lower chest and upper abdomen.

Physical examination on second entry showed temperature 104°F., pulse 90 and respirations 28. The chest showed lagging on the left, dulness, diminished breath-sounds and fine râles over the left base. The apex of the heart was displaced to the left. Sputum showed numerous type-III pneumococci and no tubercle bacilli. Haemoglobin 110 per cent; red blood cells 4,800,000; white blood cells 20,470; polymorphonuclears 82 per cent; filamentous forms 72 per cent; nonfilamentous forms 10 per cent; eosinophiles 1 per cent; lymphocytes 10 per cent; monocytes 7 per cent.

Type-III anti-pneumococcus serum, 100,000 units, was given intravenously on the day after entry but his temperature rose daily to 102°F.

The X-ray films of the chest (figure 5, A and B) showed a persistent lobar density involving the entire left lower lobe and part of the left upper lobe. On the fourth day following his entry, while his fever was still 103°F., bronchoscopy revealed a polypoid, firm, fleshy tumor one inch below the carina with a broad attachment to the mesial wall of the left stem bronchus. Obstruction was not quite complete, and over and around the tumor a stream of thick yellow pus flowed as the bronchus was dilated. Approximately two ounces of this pus

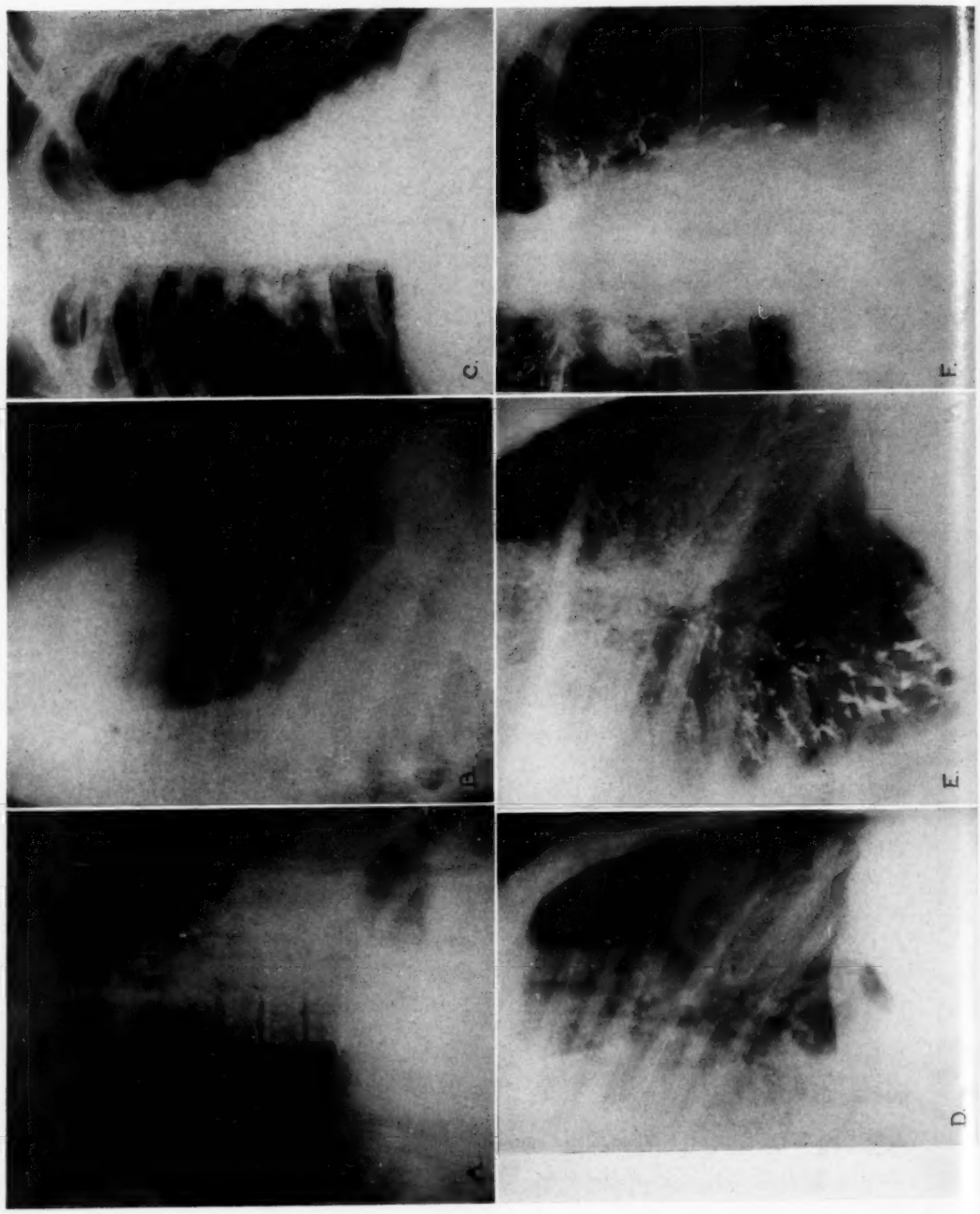

FIG. 5

as sucked out and smears showed large numbers of pneumococci only. A portion of the tumor was removed for biopsy. Several pathologists of note were consulted and each gave a different diagnosis which varied from definitely malignant neoplasm to benign neoplasm. The pathological diagnoses were small celled carcinoma; haemangioendothelioma; angiosarcoma; and benign adenoma.

For the time being it was decided to treat the tumor as benign so, at two further bronchoscopies, the tumor was removed with biopsy forceps. The symptoms of lobar pneumonia subsided the day after the first bronchoscopy, and the temperature dropped and remained normal. Follow-up after three weeks (figure 5, C and D) showed clearing by X-ray. Slight cough with mucoid sputum was still present after three months but no neoplasm was found then in bronchial biopsies. There has been a continuous and steady gain of weight to above normal. Moderate bronchiectasis in the left lower lobe was demonstrated by the bronchogram (figure 5, E and F). His general condition was excellent.

COCCIDIOIDES

Coccidioides is a disease endemic in the San Joaquin Valley of California. No specific treatment for it exists and its protean manifestations are only imperfectly understood. The clinical and pathological features of this disease closely simulate tuberculosis so that only the finding of the doubly refractile coccidioidal bodies in the sputum differentiates the two. A chronic form of the disease produces excavation which may simulate cystic disease of the lung. The case to be reported was diagnosed infected cystic disease before operation, and the true diagnosis was not revealed until the coccidioidal bodies were found in the lobectomy specimen. This is the first published lobectomy for this disease.[4]

FIG. 5

FIG. 5. Case 3. Pneumococcus type-III suppuration associated with bronchial occlusion from "benign" tumor.

A & B: May 3, 1938. Day after entry, posteroanterior and left lateral films showing displacement of mediastinum, heart and trachea to the left with consolidated atelectatic left lower lobe.

C & D: May 24, 1938. Posteroanterior and left lateral films. Clearing and aeration of left lung after endobronchial removal of the tumor. Lateral view suggests bronchiectasis in lower lobe.

E & F: July 22, 1938. Posteroanterior and left lateral films. Lipiodol shows numerous dilated bronchi in the left lower lobe. Symptoms minimal, nonproductive morning cough.

[4] In discussion of this paper, Dr. J. C. Jones reported an unpublished similar case operated upon by himself and Dr. F. S. Dolley a few months previous to this one.

Case 4: W. T., white, male, aged 40. Admitted to University of California Hospital July 13, 1937; discharged August 15, 1937. His onset was nine years before entry, with a short attack of pleuritic pain in left apex and axilla. From that time until six months before entry he had no complaints. In January, 1937, he began to have an unexplained fever and general malaise. This was followed by the onset of cough productive of several ounces of purulent sputum daily. He continued work with these symptoms until May, 1937, when he had a haemoptysis of about one tablespoonful followed by streaking for three or four days. Five weeks before entry he had another small haemoptysis but continued to work. He was referred to the University of California Thoracic Clinic in June, 1937, by Doctor Trimble, with a diagnosis of infected cystic lung.

He had lived in the San Joaquin Valley for fifteen years. Physical examination revealed a well developed and nourished white male in no pain or distress, without dyspnoea or cyanosis. Axillary lymph nodes were palpable. Chest was symmetrical, fairly well clothed, but with supra- and infraclavicular wasting, more marked on the left. There was lagging of the left upper chest. The percussion note was resonant. Tactile fremitus, breath-sounds and voice sounds were diminished over the left upper chest. Subcrepitant râles were present over this area. The remainder of the examination was negative. His fingers were not clubbed. Tuberculin tests were positive. Red cells 4.4 million; haemoglobin 86 per cent; white cells 13,300 with 80 per cent polymorphonuclears. Urine was normal. Wassermann test was negative. Ecchinococcus skin test was negative. His vital capacity was 3,200 cc. The sputum was purulent, not foul, negative for acid-fast microörganisms and elastic tissue. Diagnostic artificial pneumothorax was instituted July 14, 1937 and disclosed broad adhesions about a large excavated area in the left upper lobe. X-ray films and bronchography (figure 6, A and B) demonstrated large cystic excavations in the left upper lobe. On July 21, 1937, a left upper lobectomy was performed by Doctor Brunn. Convalescence was complicated by fever and pleural fluid which contained coccidioidal microörganisms, but the patient was discharged three weeks after operation with a draining sinus, and the lower lobe had not yet obliterated the pleural cavity.

When the diagnosis of coccidioides was made, thymol was administered. Two months after the lobectomy an *empyema necessitans* was drained of three ounces of purulent material and at this time he was quite weakened and dyspnoeic.

Pathological description by Doctor Rhinehart: Specimen (figure 6D) of left upper lobe weighs 113 gm. A cavity 4 cm. in diameter has a roughened wall. Several bronchi communicate with it. The lung around the cavity is atelectatic. There is moderate thickening of the pleura over the lateral surface.

Microscopically the cavity wall is composed of eosinophilic debris in which

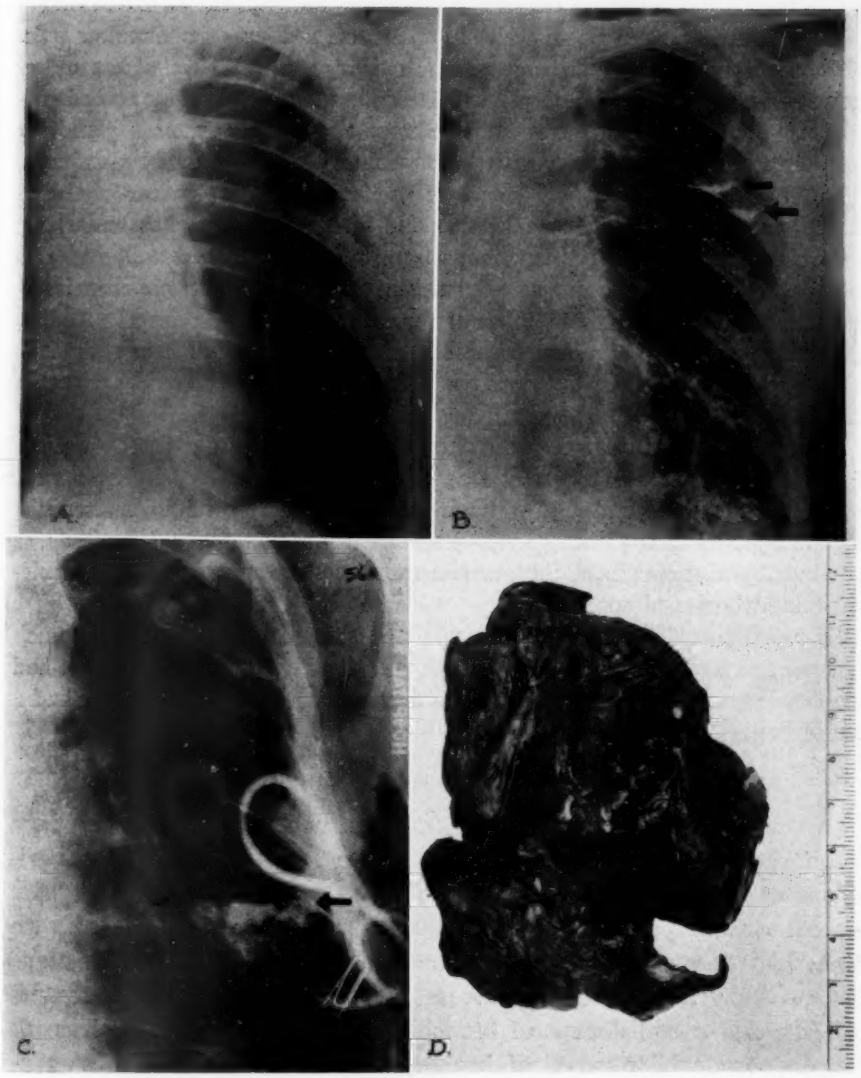

FIG. 6. Case 4. Chronic pulmonary coccidioides with excavation treated by lobectomy.

A: June 28, 1937. Markings in left upper lobe suggest cystic disease.

B: June 30, 1937. Lipiodol demonstrates two fluid levels in "cystic" areas.

C: April 21, 1938. Nine months after lobectomy. Lipiodol instilled into draining sinus in chest-wall, showing small empyema still present.

D: Lobectomy specimen of left upper lobe showing large irregular interloculating excavation. Coccidioidal bodies present in the wall of the "cyst."

are basophilic granules, the debris resting on chronic granulation tissue that is heavily infiltrated with plasma cells, lymphocytes and large mononuclear cells. The outer limits of the wall merge with pulmonary parenchyma that has undergone varying amounts of fibrosis and infiltration with lymphocytes and eosinophiles. Many alveoli are trapped in fibrous tissue and assume a glandular appearance. Tubercles are present, some containing foreign body giant cells. The large cavity has a short length of pseudostratified columnar epithelial lining which as it ends along the denuded inner cyst lining has undergone metaplasia of the stratified squamous type. Within the cyst wall and also deeper in the parenchyma, usually within tubercles or necrotic chronically inflamed areas, are seen a number of round, clear, doubly refractile bodies, some of which contain a few basophilic granules. Carbolfuchsin stain fails to reveal tubercle bacilli but does tint the outer rim of the doubly refractile bodies.

Pathological diagnosis: Coccidioidal granuloma of the lung with cavitation.

Further laboratory report by Doctor Schumacher: Microörganisms were isolated from the pleural fluid which in culture resemble coccidioides immitis. When injected into guinea pigs a generalized granulomatous infection was produced. Material from the granulomatous lesions contained the double-contoured bodies of coccidioides.

X-ray (figure 6C) follow-up in April, 1938 showed the pleural space much smaller and holding only a few cc. One year after lobectomy the patient had improved markedly in his general condition, was able to work, but still had a small sinus.

SUMMARY

A discussion of the surgical treatment of nontuberculous pulmonary suppurations is presented. This discussion is based upon the experiences at the University of California Thoracic Surgical Service with bronchiectasis, putrid pulmonary abscess, suppuration associated with bronchial obstruction from tumor, and coccidioides. Two-stage thoracotomy for pulmonary abscess, one-stage lobectomy for bronchiectasis, and establishment of bronchial drainage via the bronchoscope by endobronchial removal of benign tumors are emphasized. A successful lobectomy for pulmonary coccidioides is presented.

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PRIMARY COCCIDIOIDOMYCOSIS[1,2,3]

The Initial Acute Infection which Results in Coccidioidal Granuloma

ERNEST C. DICKSON

In 1894, Emmet Rixford (1) reported the first known case of what is now known as coccidioidal granuloma in North America, the only one known before that time having been observed in Buenos Aires (2). At first the peculiar endosporulating parasite was believed to be a protozoan and was named by Stiles *coccidiodes* because it was like coccidia (3). In 1900, Ophüls and Moffitt (4) found that it was not a protozoan but a fungus infection and the name coccidioides was retained, the fungus being called *fungus* (*oidium*) *coccidioides*, and the lesion it produced being called coccidioidal granuloma. It soon became apparent that the lesions of coccidioidal granuloma were extremely similar to tuberculosis; as a matter of fact, Rixford and Gilchrist described their first case as coccidioidal pseudotuberculosis. In 1907, Hektoen (5) wrote that coccidioidal granuloma "presents the best mimicry of tuberculosis ever seen." Smith, Cummins and Halliday (6) stated that "the gross osseous and pulmonary lesions are identical with tuberculous lesions, except that there is less tendency to pulmonary cavitation and greater tendency to widespread osseous involvement than in tuberculosis," and Jacobson (7) said "the gross clinical similarity between coccidioidal granuloma and tuberculosis is so close that a positive differentiation between the two is only possible by laboratory methods." In 1929, I published a short report entitled *Mimicry of Tuberculosis by Coccidioidal Granuloma* (8) in which I pointed out that not only were certain cases of coccidioidal granuloma singularly like tuberculosis, but that it was not infrequent for cases to be diagnosed as tuberculosis clinically and on gross examination at autopsy, only to find that the true diagnosis was coccidioidal granuloma when sections of the tissues were examined under the microscope.

[1] Read as part of the Symposium on *Chronic Nontuberculous Infections of the Lung* at the joint session of the Pathological and Clinical Sections at the 34th annual meeting of the National Tuberculosis Association, Los Angeles, California, June 21, 1938.

[2] From the Department of Public Health and Preventive Medicine, Stanford University School of Medicine, San Francisco, California.

[3] This study is being aided by the Rosenberg Foundation, San Francisco.

As time went on, it became apparent that in the United States the one main endemic focus is the San Joaquin Valley in California where the great majority of cases in North America originate. Although a few cases have been recognized in other parts of the United States, in 1931 Beck (9) reported that among 296 cases of coccidioidal granuloma which had been reported, 254 had originated in California, 14 in South America, 2 in Italy, and 16 in other states of the Union. There is record that some of the 16 had not been in California. By 1936 (10) there was record of 450 cases in California of which 224 had died, and of which 350 had originated in four counties of the San Joaquin Valley and the adjacent Los Angeles County. The only other region in which many cases are known to occur is in Brazil.

More recently it has been found that not only human beings may become infected with coccidioides fungus but also certain domestic animals, for example, cattle and sheep. The first beef animal was reported by Giltner (11) in 1918 but more recently Beck (12), Traum (13), and Beck, Traum and Harrington (14) reported sixteen cattle and one sheep which had been found in the abattoirs of southern California. In 1937, Davis, Stiles and McGregor (15) reported 7 cases of bovine coccidioides which had been slaughtered in Los Angeles, having come from feeding farms in Kern County, and in 1938 (16) they reported 23 calves from Madera County, also slaughtered in Los Angeles, which had coccidioides infection. It thus follows that cattle are not unusually infected in the same general region as human beings.

During the whole time that coccidioidal granuloma has been under observation, there has been no indication as to how the disease is transmitted to man or to domestic animals. Although the disease is without doubt infectious, there has been no record of man-to-man or animal-to-man infection. Various media of infection have been considered, even passage of the virus through insect bite, but nothing has been found which could explain how the majority of individuals acquire the disease. A few patients give a history of primary infection through a break in the skin as produced by a prick from a cactus spine or an abrasion from picking walnuts, where the initial lesion appeared at the site of injury, but the great majority of cases give no such history. The way in which the disease is transmitted has for years remained a mystery. In 1929, Doctor Ophüls said, while discussing a report by Pulford and Larson (17), "All evidence so far gathered seems to point to respiratory involvement with primary localization of the virus in the lung. . . . It is probably

the spores of the fungus growth that become mixed with dust and are then inhaled into the lungs. The finding of the disease in animals such as cattle and sheep does not seem to me to suggest that the infection is from animals to human beings. It is much more likely that the animals contract the disease much in the same way as the human beings do in the infected region."

Proof that the inhalation of chlamydospores may cause coccidioides infection was established by an accident in our laboratory in 1929 (18). A young man who was commencing work with coccidioides fungus inadvertently opened an old petri dish culture which he proposed to use. When the cover glass of the petri dish was removed, he noted a fine cloud arise from the old culture. Nine days later he became ill with a symptom complex which has been found to be very common in the San Joaquin Valley, the region from which approximately 85 per cent of the known cases of coccidioidal granuloma in the United States have originated. Like the great majority of similar cases in the San Joaquin Valley, the young man recovered without complications and is now apparently well, nine years later. Shortly after this first case, another young man, from near Bakersfield in the San Joaquin Valley, was also under the care of Dr. P. H. Pierson, suffering from a very similar illness. The major difference between the two cases was that in the first case there developed erythema nodosum but, in the second case, no erythema nodosum was seen. From both cases, cultures of sputum gave growth of fungus coccidioides which was proved virulent by guinea-pig inoculation. Like the first case, the second young man recovered promptly from the acute illness.

It has been found that a symptom complex like that of the first of these patients is very common in the San Joaquin Valley in California; so common, in fact, that it is popularly known among the laity as "Valley Fever" or "Desert Fever." Persons of all ages and of both sexes may be affected; they are usually ill from three to six weeks, and then recover without any complications. Many of them apparently are not sufficiently ill in the beginning to call for medical aid; as a matter of fact, it is often pain from erythema nodosum which brings them to a physician. From a questionnaire sent to the practicing physicians in the San Joaquin Valley, 75 physicians reported that they had seen 354 cases of erythema nodosum or Valley Fever between January 1, 1936, and May, 1937, 353 of which had recovered without complications and one of which had died of coccidioidal meningitis.

At the onset of the acute illness the patient often describes it as a bad cold or "flu." There is often general malaise with fever and sometimes with general aches and pains. Sometimes the illness is described as pleurisy. There may be rapid loss of weight up to fifteen or twenty pounds; sometimes there are chills and sweating. There may be fever up to 100° to 104°F. Often the bronchitis is relatively slight but usually there is mucopurulent sputum which is sometimes streaked with blood. Sometimes the patients improve so much within a few days that they feel they are getting better, but within from eight to fifteen days after the onset there is an eruption of skin lesions, which are popularly known as "the bumps" which are most common on the shins and are typically erythema nodosum. Similar lesions may appear on the thighs, buttocks, trunk and upper extremities, when they may be described as erythema multiforme. They do not fluctuate or suppurate but may be fiery red and very tender or painful. It is not unusual that it is the painfulness of the erythema nodosum which first brings the patient under medical care. Within from 48 to 72 hours the lesions become purplish and begin to fade and disappear within a few days leaving only a more or less persistent brownish discoloration of the skin. It is only after erythema nodosum has appeared that the disease is known as Valley Fever or Desert Fever.

If roentgenograms of the chest are taken during the acute attack, it will usually be found that there are dense shadows in the hilar regions which indicate enlargement of the hilar lymph nodes. Radiating out from the hilar region and more or less widely distributed through the lung area are densities indicating parenchymatous involvement in various parts of the lung, which may occur in all the lobes. The X-ray diagnosis is very often tuberculosis on the first examination, but as time goes on these areas of increased density clear up so rapidly that, after a few weeks, the lungs may appear entirely clear. Occasionally patients with such pulmonary shadows have been sent to sanatoria for tuberculosis, where it has been impossible to prove tuberculosis by recovering acid-fast bacilli or by tuberculin tests.

When sputum of such patients is examined it is not unusual to find the typical spherules of coccidioides. Cultures show the typical coccidioides fungus and when guinea pigs are injected, they develop coccidioidal granuloma. Seventy-two of one hundred and twelve specimens of sputum sent to our laboratory from such patients have proved positive for coccidioides infection. It should be remembered that, as in tuber-

culosis, the infecting microörganism may be recovered by washing the stomach of a child who is too young to raise sputum. We have studied several such cases and the typical spherules were seen in the mucopurulent sputum recovered by lavage, cultures showed growth of fungus coccidioides and the microörganism was proved virulent by guinea-pig inoculation.

Examination of the urine shows what is usual in febrile conditions. The leucocyte count varies from about normal to 15,000, but at times, often associated with the erythema nodosum, there may be eosinophilia. The highest eosinophilia we have seen was in a patient whose leucocytes varied from 8,000 to 13,500, in whom there were 4 per cent eosinophiles on admission, 16 per cent on the eighth day of illness and 4 per cent again on the eleventh day. We have had opportunity of making sedimentation tests on three patients and found 31, 32 and 45 mm., respectively, in sixty minutes.

The use of the coccidioidin skin test in cases of Valley Fever has been most helpful in correlating the diagnosis with coccidioides infection. It has been found that the reaction of Valley Fever patients to coccidioidin is much more violent than in cases of coccidioidal granuloma. As a matter of fact, the size of the dose for intracutaneous injection was stated by Jacobson (7a) to be 0.3 cc. of the undiluted filtrate for diagnosis of coccidioidal granuloma, but so large a dose has proved entirely too strong for Valley Fever. In fact, it may cause immense oedema and necrosis of the skin in such acute cases. We have found that 0.1 cc. of 1 to 1,000 dilution of a lot of coccidioidin we have prepared is adequate and produces well marked reactions, sometimes with vesicle formation. For coccidioidal granuloma, 0.1 cc. of 1 to 10 dilution is the required dose with this antigen. This corresponds to the experience of Wallgren (19) with tuberculin in primary tuberculosis. He reports that among children with erythema nodosum in primary tuberculosis, the sensitivity to tuberculin may be as high as to 0.000,001 mg. tuberculin, whereas in tuberculous children without erythema nodosum, there were only 3 of 321 children who had sensitivity to 0.001 mg.

But there are also cases of primary coccidoides infection which differ only in the fact that they have no erythema nodosum and, therefore, are not considered as Valley Fever patients. It has been found that these, too, may have fungus coccidioides in the sputum and the characteristic changes in the lungs as shown by X-ray. They may be diagnosed as "flu" or bronchopneumonia and may recover promptly from

the acute illness. As in the Valley Fever patients, that is, those with erythema nodosum, some of these patients may progress to typical coccidioidal granuloma. We have seen one such patient in the hospital who has apparently recovered and we have record of several who developed coccidioidal granuloma, as well as some who developed coccidioidal granuloma following Valley Fever. At the present time, there is no knowledge as to how frequently the acute infection may occur with or without erythema nodosum, or whether either group is apt to be more often followed by coccidioidal granuloma than the other.

It has been mentioned that coccidioidal granuloma may closely similate tuberculosis clinically and pathologically. Only by recognition of the parasite of coccidioides or the tubercle bacillus may the lesions be differentiated in many cases. One other feature tends to correlate them further. In autopsies of persons who have died of various diseases, it is not rare to find healed lesions of coccidioides infection in the parenchyma of the lungs or in the peribronchial lymph nodes which clearly recall the characteristic Ghon's bodies of tuberculosis. In the primary infection with coccidioides, the onset is with respiratory infection with fever, bronchitis and frequently with pleurisy. Erythema nodosum is a very common accompaniment. X-ray films of the chest show indication of transitory involvement of the parenchyma of the lungs and involvement at the hilum. Wallgren (20) says that "Histologically regarded the pneumonia (of primary pulmonary tuberculosis in childhood) does not have the appearance of tuberculosis." In primary coccidioides infection, at least in animals which have been made to inhale the chlamydospores, there is nothing resembling the granulomatous structure in the lungs, only a diffuse interstitial pneumonia which clears promptly. There is a specific skin test for coccidioides infection as in tuberculosis and the reaction is much more violent in the primary acute infection than in the later stage of coccidioidal granuloma. As in tuberculosis, in the acute infection with coccidioides the sensitization reaction to coccidioidin does not develop until several days after the exposure to infection; in guinea pigs and rabbits it is from six to ten days after the chlamydospores are inhaled. In acute coccidioides infection, as in primary tuberculosis, only a small number of the victims progress to coccidioidal granuloma.

It is, therefore, definitely established that infection with coccidioides fungus is caused by the chlamydospores of the vegetative phase of the fungus which in some way gain access to the tissues. There seems to

be no doubt that the chlamydospores are carried through the air, presumably associated with dust. When primary skin lesions follow trauma of the skin as by the prick of the skin by a cactus spine or by abrasion of the skin caused by picking walnuts, etc., undoubtedly the chlamydospores are associated with the dust on the offending objects. In general, however, primary coccidioides infection seems to be acquired by inhalation of the chlamydospores and the development of the primary lesions is in the lungs or regional lymph nodes. Thus can the occurrence of coccidioides lesions in animals in the endemic areas as well as in man be rationally explained. The development of the later coccidioidal granuloma is undoubtedly secondary and is caused by migration of the virus to different parts of the body from the primary foci in the lungs or peribronchial lymph nodes, presumably by the blood-stream.

It follows, therefore, that infection with coccidioides fungus may be manifested in at least two ways: a primary acute respiratory infection, often accompanied by erythema nodosum, from which the great majority of patients recover without complication, and a later more or less chronic granulomatous disease, known as coccidioidal granuloma, which may be very disabling and has a case mortality rate of approximately 50 per cent. It therefore becomes necessary to have a name for coccidioides infection to include both types of illness. In a previous report (18), I have suggested the term coccidioidomycosis which may be classified as primary for the acute initial infection, and progressive or secondary for the coccidioidal granuloma stage. The latter may be further subdivided to indicate the regional distribution of the lesions if desired; for instance, of the skin, bone, meninges, lungs.

SUMMARY

The primary type of infection with coccidioides fungus has been described.

The great majority of infected persons recover promptly without complication.

A very large percentage of patients have erythema nodosum.

Coccidioidin (the specific skin test antigen) skin tests are relatively violent in the primary cases.

Cases with or without erythema nodosum may progress to coccidioidal granuloma.

The mimicry of tuberculosis in the primary stage, as in the later progressive coccidioidal granuloma, is most striking.

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PNEUMONITIS[1,2]

MAX PINNER[3]

The term pneumonitis has met with much disfavor both from clinicians and pathologists. It is stated justifiedly that it means inflammation of the lung and that pneumonia is the generally accepted term for this condition. There are no valid arguments against this. But the term pneumonitis, once it is endowed with a definite and specific meaning, may well be found convenient. It is proposed that pneumonia signify all those acute inflammatory changes of the lung that are usually self limited, that are characterized mainly by an intraälveolar exudate, with or without minor and secondary changes in the interstitial tissue, and that customarily heal without leaving any significant damage in the lung. Pneumonitis may, then, be used to designate those inflammatory changes in the lung that have a prominent tendency toward chronicity and recurrence, that are characterized by profound changes in the interstitial tissue and in the bronchi (in addition to intraälveolar exudate), that usually lead to permanent structural changes in the lung and in which suppuration and fibrosis are invariably present.

History, symptomatology, clinical course, indications for treatment, prognosis, pathogenesis and pathology are so radically different in the two groups of diseases that a terminological differentiation would seem to be helpful. It is obvious, and needs hardly further emphasis, that there is no sharp dividing line between pneumonia and pneumonitis; while the majority of cases in each group are clearly defined according to the criteria mentioned, such clinical observations as unresolved lobar pneumonia, postpneumonic abscesses, etc. indicate the occurrence of border-line cases.

A valid objection to the use of the term pneumonitis is that the clinical entities that, according to this suggestion, belong in the group pneumonitis are all already designated by descriptive and time-honored

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[2] This is a summary of two papers read before the Eastern Section of the American Sanatorium Association, Scotch Plains, New Jersey, November 12, 1937, and before the New York Society for Thoracic Surgery, New York City, November 26, 1937.

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names, such as pulmonary abscess, gangrene, bronchiectasis, foreign body pneumonia, etc. However, the term pneumonitis is recommended because such a generic term, comprising these various diseases, will help to emphasize the essential characteristics that these conditions have in common and it will provide a much needed designation for the basic morbid changes that regularly coexist with or precede the development of the fully developed and well recognized lesions of abscess, gangrene, bronchiectasis, etc.

The need for bringing into clear focus the basic similarities in these processes and the desirability of a well defined generic term grew out of several observations: (*1*) the essential similarity in pathogenesis, (*2*) the fact that more often than not abscess, bronchiectasis and other bronchial changes, gangrene, focalized fibrosis are found in the same lung, although both the clinical and pathological picture may be completely overshadowed by *one* of these features, (*3*) that a lesion, for which I do not know any more descriptive term than suppurative and organizing pneumonitis, is regularly demonstrable in these lungs, (*4*) that profound bronchial disease—this in contradistinction to pneumonia and to tuberculosis—is always present.

Omitting embolic pulmonary abscess from the discussion, it need only be mentioned that pneumonitis in all its forms is initiated by aspiration of infectious material. Such aspiration into the pulmonary parenchyma causes localized pneumonitis. The modality of the aspiration on one hand and the available pulmonary defense on the other hand determine the eventual outcome, not only in regard to prognosis but much more significantly so in respect to the particular structural end result (that is, fibrosis, abscess, bronchiectasis, etc.).

Under modality of aspiration consideration must be given to the following points:

1: Massive single aspiration, most likely to lead to abscess formation.

2: Small, chronically repeated aspirations, such as may occur from infected mouth, tonsils or sinus, most likely to lead to bronchiectasis or chronic organizing, recurrent pneumonitis.

3: The type of microörganisms aspirated, determining within certain limits the severity of the response and the development of pyogenic necrosis (abscess) or apyogenic necrosis (gangrene).

Massiveness of aspiration refers primarily not to the number of microorganisms but to the amount of the aspirated material; this determines

the eventual localization, the possibilities of its more or less complete expulsion and the degree of interference with bronchial drainage.

The importance of the state of the pulmonary defense is obvious in patients with abscess following aspiration during anaesthesia, intoxication or following large doses of hypnotics. Less obvious but equally important are all and any conditions that impair either the cough reflex, the expulsive force of cough or free bronchial drainage, such as damage to pulmonary tissue from previous disease, fibrosis, emphysema, pleural adhesions, impairment of respiratory musculature, for example, by postoperative pain and any type of bronchial obstruction. Aspiration is not enough; the aspirated material must in whole or in part be retained in the lower airways; to what extent this happens is determined by the nature of the aspirated material and the state of the pulmonary defense. Retention is recognized as an outstanding pathogenetic factor in experimental work and clinical observation.

The early response to retained infectious material is an acute exudative inflammation, the exudate involving intraälveolar spaces, interalveolar walls, and quite predominantly the interstitial tissue in septa, around bronchi and blood vessels. Involvement of the entire wall of bronchi is frequent. In the advanced stages of the lesions observed in autopsy or surgical specimens, the exudate is in distribution and composition much less homogeneous than that of pneumonias. Due to continuous or intermittent progression of the lesions, even in the material available for pathological studies, early phases are regularly found. In all but the most acute cases, the intimate intermixture of acute and chronic phases is one of the outstanding characteristics. The profound involvement of the interstitial structures, seen already in early lesions, explains why permanent and crippling damage is done. The walls of small bronchi and bronchioles are destroyed by suppuration and alveolar and bronchiolar walls undergo necrosis (figure 1). The two dominant features are apparent—suppuration and organization.

Organization takes place both in the intraälveolar and in the interstitial exudate (figure 2). Its eventual result is fibrosis and secondary emphysema (figure 3). Within large fibrotic areas small residual abscesses are frequent (figure 5). Often the fibrosis is particularly massive in the interlobular septa and peribronchially (figures 4 and 11).

But, to emphasize once more: the coexistence in one lung of acute and chronic processes, of pneumonitic suppurative infiltration, panbronchitis, abscess formations, gangrenous areas and bronchiectatic changes, is probably the most characteristic finding in these cases of pneumonitis.

This is particularly impressive on histological studies when—examining a large number of different blocks—the dominance of *one* type of grossly visible lesion disappears. It is, for example, impossible to find a lung that shows only bronchiectasis, although this may be clinically and gross-anatomically the outstanding lesion. But on closer examination there are always areas of parenchymal suppuration, fibrosis, emphysema and frequently of gangrene (figure 7).

Bronchial involvement, as stated before, is invariably present. The great variety of structural changes in the bronchi is undoubtedly a potent factor in the self-perpetuating nature of the disease because these changes cause retention of inflammatory products. Interference with drainage is brought about by any of the existing bronchial changes: by simple thickening of the mucosa through cellular infiltration (figure 6), leading to considerable stenosis of the lumen; by desquamative and atrophic bronchitis, impairing the ciliary motion; by atrophic or fibrotic changes in the bronchial musculature, inhibiting the intrinsic bronchial movement; by destruction of the elastic (figure 10) and cartilaginous elements (figure 8), impairing the elastic properties of the bronchial wall; by massive peribronchial fibrosis (figure 4), leading to extrinsic stenosis; by bronchiectatic dilatation, establishing pools of septic material, frequently peripheral to stenosed bronchi.

In the discussion of the pathogenesis of bronchiectases, atelectasis has occupied a prominent place, particularly during the last few years. It is obvious that a number of different pathological conditions are called atelectasis by various authors and that this term is frequently used in a vague and ill defined manner. Terminological accuracy would undoubtedly help to clarify this subject.

The scientific usage of the term atelectasis has long since departed from its etymological derivation: ateles = incomplete, ectasia = expansion. Atelectasis denotes in common pathological usage airlessness of otherwise normal pulmonary parenchyma and not incomplete expansion. Reduced air content of lung tissue is called pulmonary collapse; incomplete atelectasis is a *contradictio in adjecto*. If the air in lung tissue is replaced by something else, for example, by inflammatory exudate, by transudate or by scar tissue, such airlessness should not be termed atelectasis; the medical vocabulary contains for these conditions the accurate and descriptive terms of pneumonia, pulmonary oedema and fibrosis, respectively.

It is firmly established that atelectasis occurs spontaneously only through cessation of respiration in a lung whose circulation continues.

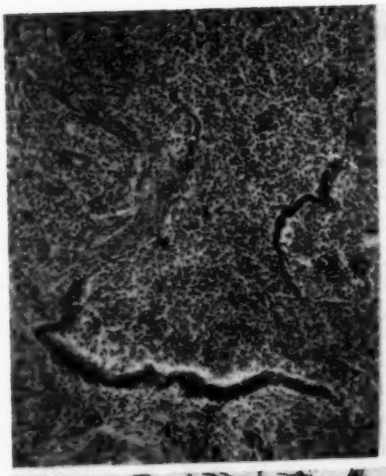

FIG. 1

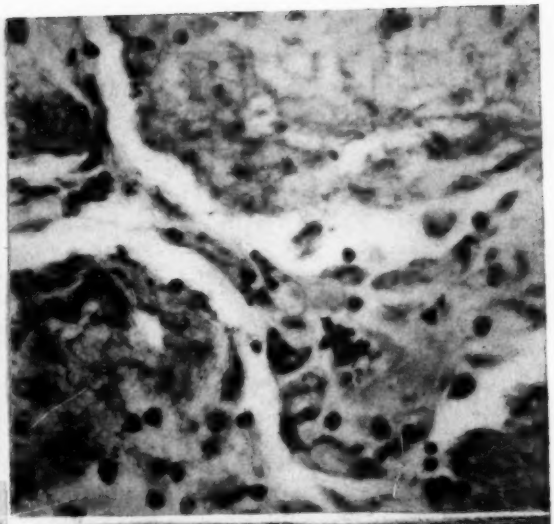

FIG. 2

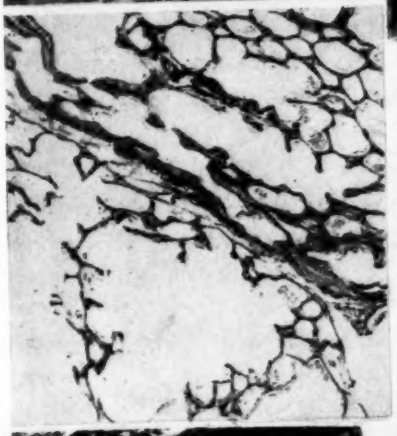

FIG. 3

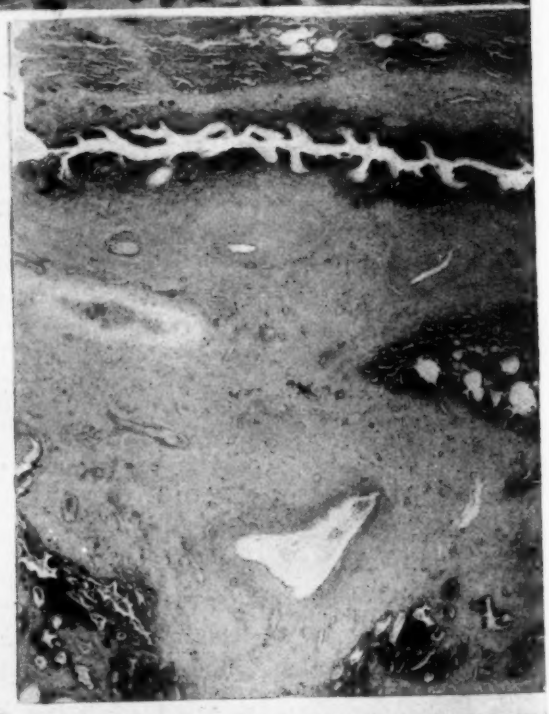

FIG. 4

FIG. 5

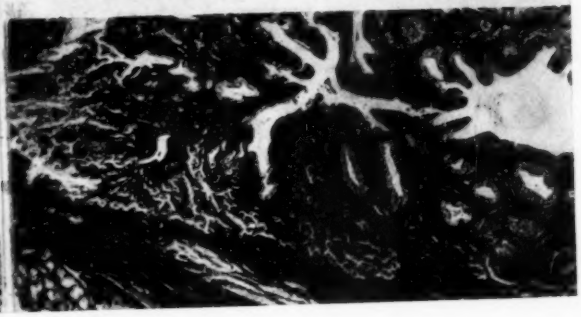

FIG. 6

FIGS. 1–6

This occurs only under two conditions: (*1*) bronchial obstruction, and (*2*) increase in intrapulmonic pressure remaining equal to or above atmospheric pressure during the entire respiratory cycle, making respiration impossible.

When bronchial occlusion occurs, the intrapleural pressure sinks to a sufficient degree to cause pulmonary oedema and bronchial drainage is impaired. These two consequences of bronchial obstruction lead sooner or later to pneumonitis, particularly in a lung that is the seat of a previously established infectious process.

Obstructive atelectasis in the pathogenesis of pneumonitis and bronchiectasis is a mental abstraction, it does not exist in reality, save possibly for short periods between actual bronchial occlusion and the development of the secondary changes just mentioned.

Careful clinical observation confirms the statement that the lasting and significant consequence of bronchial occlusion is not atelectasis but pulmonary oedema and pneumonitis.

If bronchial occlusion exists only for a short period in the presence of a noninfected lung (postoperative massive collapse, early removal of foreign bodies), pneumonitis, as a rule, does not develop, but the phase of pulmonary oedema is clinically demonstrable in many of these cases.

In pneumonitic lungs removed at autopsy or operation, atelectasis in the strict sense of the word, as defined above, is never seen. Furthermore, all evidence points to the conclusion that atelectasis *per se*, such as seen in lungs under high-pressure pneumothorax or following radical thoracoplasties, does not produce fibrosis; the latter is the eventual result of inflammation. Shrunken bronchiectatic lobes are not atelectatic, but suppurative and more frequently fibrotic. The clinical and particularly the roentgenological signs and symptoms of atelectasis, save suddenness of onset, are essentially similar in the presence of a true atelectasis and in a massive, localized fibrosis.

FIG. 1. Suppurative lesion in pulmonary parenchyma and in a bronchiole whose wall has been partly destroyed. H.E. ×120

FIG. 2. Incipient organization of intraälveolar and interalveolar exudate. H.E. ×660

FIG. 3. Diffuse fibrotic thickening of alveolar walls and interstitial tissue and secondary emphysema. H.E. ×80

FIG. 4. Massive perivascular and peribronchial fibrosis causing constriction of bronchus. H.E. ×17.7

FIG. 5. Multiple miliary abscesses in fibrosed pulmonary tissue adjacent to a bronchiectatic cavity. Mallory. ×17

FIG. 6. Massive cellular infiltration in bronchial mucosa causing marked reduction of bronchial lumen. Mallory. ×17

FIG. 7

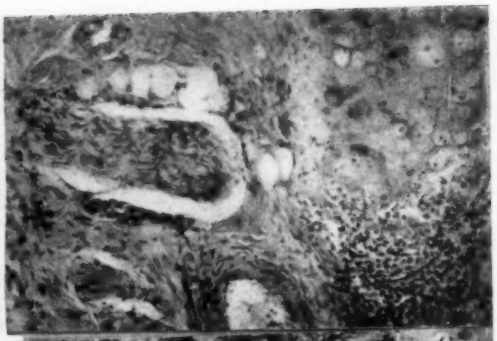

FIG. 8

FIG. 9

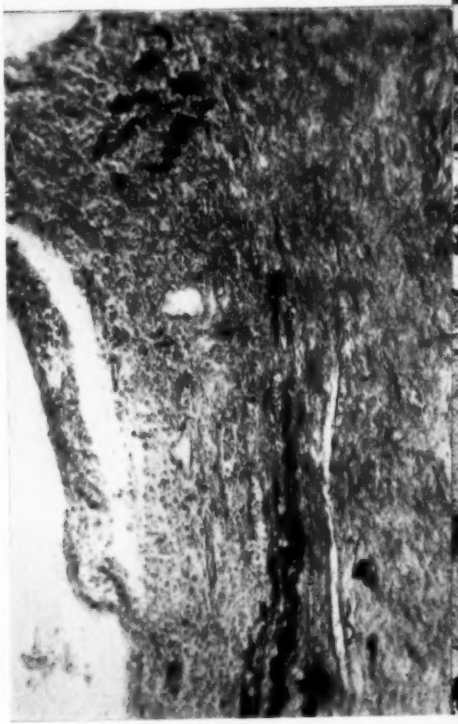

FIG. 10

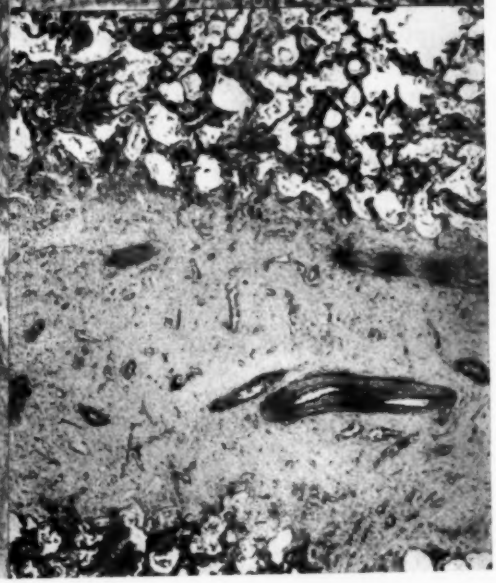

FIG. 11

FIGS. 7–11

It is not doubted that the physical forces operative following bronchial occlusion act in the direction to dilate bronchi. Histological examination of bronchiectases indicates that profound structural changes of the bronchial walls are always present, and it seems likely that dilating physical forces are effective only if damage of the bronchial wall is established. It has been mentioned above how every layer of the bronchial wall is involved in the inflammatory process and its resulting necrosis and fibrosis. It is probably significant that not infrequently nerve fibres are involved and that, as mentioned by Hanot and elaborated by Lemoine, occlusion and thrombosis of branches of the bronchial arteries are frequent (figure 9). While interference with the nutritional artery must be an important pathogenetic feature, it does not seem safe to assign to it the leading rôle.

The correct evaluation of bronchial disease forms the basis for therapeutic indications. As soon as the bronchial changes interfere with proper drainage of parenchymal and intrabronchial suppuration, spontaneous healing cannot be expected. The alternative between chronic pulmonary disease and surgical intervention must be faced.

At this point the observations and opinions discussed gain practical importance. Bronchiectasis is never an isolated lesion surrounded by normal pulmonary parenchyma; the latter is always the seat of pneumonitis, suppurative or organized or both, playing a decisive rôle in the chronicity, the exacerbations and the incurability of bronchiectases. Conversely a pulmonary abscess or any suppurative disease of the lung is always associated with disease of the bronchi which prolongs the duration of the primary lesion or prevents completely its spontaneous regression.

It would appear justified and probably of real practical importance to designate diagnostically all the lesions discussed as pneumonitis and to add as a modifying term the clinically predominant lesion.

FIG. 7. Wall of a gangrenous cavity from a case in which bronchiectasis was the main lesion. H.E. ×170

FIG. 8. Invasion of bronchial cartilage by inflammatory exudate (bronchiectasis). H.E. ×150

FIG. 9. Thrombosis and recanalization of a branch of the bronchial artery in the wall of a bronchiectatic cavity. Weigert-van Gieson. ×150

FIG. 10. Destruction of the elastic lamella in a bronchus by granulation tissue. The bronchus was much dilated, and, as seen in the photomicrograph, the epithelium is desquamated and the mucosa shows dense purulent infiltration. Weigert. ×150

FIG. 11. Massive fibrosis of interlobular septum in a case of lung abscess. H.E. ×17.7

THORACOPLASTY IN THE TREATMENT OF PULMONARY TUBERCULOSIS[1]

Experience of French Clinics

A. MAURER[2] AND EUGENE DE SAVITSCH[3]

The skepticism of medical men in France prevented, until recently, the wide application of thoracoplasty in the treatment of pulmonary tuberculosis. As a matter of fact, the first Thoracic Surgery Service was organized by Proust, Lardennois and the senior author of this report only ten years ago in the Laennec Hospital in Paris. The service takes care not only of the patients of Paris but also of the many suburban districts and of several sanatoria in the provinces. As the methods of diagnosis, analysis and surgical technique are always under the same direction, it is felt that the evaluation of the results is comparatively easy.

In this report no attempt will be made to cite any experiences but our own. The admirable work of Alexander, Graham, Archibald, Eloesser and Coryllos are sufficiently known and appreciated to warrant special mention here.

The conservatism of French physicians, though very discouraging at first, later on proved to be beneficial to the development of the Service. Every precaution had to be taken regarding diagnosis, indications and technique, as the loss of a patient was regarded with undue apprehension. The encouraging results achieved with the first group secured wider co-operation and now this treatment meets with greater and greater approval.

In the selection of patients a complete collaboration of the physician is considered essential. The physician not only has to study the case with the surgeon but he is also expected to be present at the operation, giving his suggestions as to its execution. The after-care is in the hands of both the physician and the surgeon, thus ensuring the greatest degree of safety.

In this connection the rôle of the sanatorium is most important. A great percentage of the patients are sanatorium cases, and we feel that

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sanatorium care before and after the operation is almost indispensable. In fact most of our sanatoria have operating facilities, thus permitting us to carry out all our procedures right on the spot.

Our conception of thoracoplasty may be best defined by saying that it is *un modelage de la paroi thoracique*—the modelling of the thoracic wall. It is never an operation involving the use of force nor is it an operation in which active compression is hoped for. The results achieved depend entirely on the natural retractility of the tissues (1). The lesions, due to their usual retractile tendencies (5) as well as to the elasticity of the surrounding parenchyma, shrink and thus rapid healing is encouraged. It follows, therefore, that the extent of an operation depends entirely on the extent and the location of the lesion, and the surgeon is not justified in removing any more supporting structures than is absolutely necessary. We find that, in exceptional cases, it is even possible to achieve successful results by merely removing the first rib (2).

For the sake of convenience, the indications for thoracoplasty will be considered under three headings:

1: The "pulmonary" where the lesions are limited to the lungs alone
2: The "pleuropulmonary" where both the pleura and the lungs are involved
3: Strictly "pleural" thoracoplasty where the procedure is carried out only for the sake of the pleura; cases in which the pulmonary focus is either absent or completely arrested

As may be surmised the first group is by far the largest and accounts for about 84 per cent of the cases (3). In selecting the patients for the operation the surgeon must be guided by the principle that thoracoplasty must be reserved for the cases with stabilized lesions and in fairly satisfactory physical condition. Thoracoplasty on a patient with a progressing lesion seldom gives gratifying results and it is our experience that such cases invariably do better when treated by simple rest cure. Thoracoplasty should not be undertaken when pneumothorax is possible. Pneumothorax remains the least traumatic and most efficient of the various collapse operations (4).

Thoracoplasty should be considered in cases where there is a symphysis of the pleura, where partial pneumothorax cannot be improved either by the Jacobaeus operation or by phrenicectomy, or where phrenicectomy cannot give the desired results. Phrenicectomy is seldom successful:

1: When there is a large cavity at the apex
2: Where there is a cavity adhering to the thoracic wall

3: Where there is an old cavity with considerably thickened wall
4: Where there is extensive cavitation at the apex
5: Where there are disseminated fibroulcerative lesions of the entire lung

Thoracoplasty may be undertaken without hesitation where lesions are unilateral and do not show any evidence of progression, where the condition of the patient is satisfactory, and where there is some tendency to retraction. It is rare that we see the lesions limited to one side, but we do not consider the presence of contralateral lesions a serious obstacle unless they show definite evidence of activity. The study of serial X-ray films is the method of choice in reaching the decision.

Other contraindications for thoracoplasty have all to do with the basic principle which was already laid down, namely, do not touch active lesions. It is especially undesirable to operate in cases where there is evidence of recent spread around the main lesion. In cases where the principal lesion is fairly stabilized, but where there is some evidence of active process on the "good" side, the operation may be undertaken only after a selective collapse of the diseased area on the "good" side demonstrates that the process is well under control. This "prophylactic" contralateral pneumothorax was found to be a very useful expedient in many of our doubtful cases (3). Where contralateral partial pneumothorax is of some duration it is well to reduce it temporarily before undertaking thoracoplasty so as to get a clear idea of the state of the activity of the lesion. In cases where the lesion appears to be fairly well stabilized only a minimal collapse should be maintained, this permitting the greater physiological functioning of the lung.

Age as a contraindication is still fairly uncertain. We have successfully operated on several children under fourteen obtaining excellent clinical results with but a slight mutilating effect on the skeleton. We entirely agree with O'Shaughnessy (4) that thoracoplasty is contraindicated on persons over the age of fifty. However, the thoracoplasty of purely pleural indication should be carried out irrespective of this consideration.

The general condition of the patient deserves a great deal of consideration. Obese or thin patients are poor risks; weight charts should always be studied carefully and if there are some rapid changes, the procedure should be delayed until the condition becomes more stabilized. Fever should be regarded with suspicion; normal temperature for four to six weeks is very desirable before anything is undertaken. The only group

of patients with fever where no hesitation is necessary is where the X-ray shows no progression of the lesion, but where the fever may be attributed to either the retention of sputum or suppuration. Dyspnoeic patients are very discouraging. The shortness of breath may be due not only to the tuberculous process but also to sclerosis or emphysema, and thoracoplasty, which of necessity will limit respiration further, may prove fatal in such cases. Pallor of the face is also a reason to be careful. A pale face usually indicates poor resistance or a toxic condition and, therefore, nothing should be undertaken without carefully going into the patient's history with special reference to the bones, kidneys or intestines. Occasionally an unsuspected tuberculous focus may be found in one of these places. The tuberculous involvement of other tissues besides the lungs represents grave danger if it shows evidence of activity. Not infrequently in these cases thoracoplasty may be followed by generalization of the disease or by tuberculous meningitis. On the other hand tuberculous laryngitis is not a contraindication unless it reduces the patient to a state of malnutrition. In fact, not infrequently, a considerable benefit may be derived from the procedure.

The retractility of the lesions may be determined by X-ray studies. In old lesions there may be evidence of displacement of the trachea or actual approximation of ribs in the neighborhood of the cavity. In very recent lesions, the determination of retractility is more difficult; nonetheless the assumption that they may be retractile is fairly safe.

The thoracic surgeon must also keep in mind that pulmonary tuberculosis is a disease that has a cyclical tendency of development and he must therefore make an attempt to operate on the patient when his condition is fairly stabilized. It is undesirable to do anything when the patient is either rapidly improving or when he is getting worse.

In determining the actual surgical procedure it must be kept in mind that this procedure in no sense can be standardized and that the number of stages in which it is to be carried out is determined entirely by the condition of the patient. In the majority of cases the most successful results are achieved in several stages. In our series of 518 cases, 1,342 operations were performed, averaging roughly three stages for each patient (6).

The tuberculosis patient is fundamentally fragile and we should not expect too much of his resistance. It is not desirable to obliterate in a single procedure a large focus as this may be followed by a fatal spread. In a number of cases where too much optimism was expressed regarding

the resistance of the patient, the operation was followed by reactivation of other foci.

The surgical approach depends entirely on the rib or its portions which we wish to remove. Usually the paravertebral approach is most useful. In 1,342 operations, the paravertebral approach was used 1,052 times. The most frequent approach is the posterior paravertebral, which accounts for 80 per cent of our cases. Either the parasternal or axillary approach was used in the remainder of the cases.

Whatever the lesion or its position, we feel that we are not justified in using any other anaesthetic than local. Local anaesthesia is desirable not only because it forces the surgeon to be more careful in carrying out his assignment, but also because it permits him to judge the condition of the patient, and the patient can continue to expectorate during the operation.

No attempt will be made to discuss in detail our technique. For this we refer the reader to our previous publications (7, 8, 9, 10, 11).

The treatment of the periosteum, however, deserves special mention. We advocate localized destruction of the periosteum. Unlike the surgeons of the Italian School, we feel that it should be limited to the dorsal portion of the ribs. The anterior part should be allowed to reossify. Unlike those in the back, the muscles of the anterior chest-wall cannot be considered as a protection against external trauma. The periosteum may be destroyed in three ways: (*1*) by removing it together with the ribs; (*2*) by doing subperiosteal resection and subsequently removing periosteum with intercostal tissue; (*3*) by application of 10 per cent formalin.

The third method in spite of the vasodilatation and consequent increase in bleeding as well as the subjective feeling of oppression is considered to be the best. Care should be taken to apply formalin gently and immediately after its application to use a dry sponge.

RESULTS

The evaluation of results is of special interest as they reflect the success with different techniques that were being tried out. In the first series of thoracoplasties, covering the period of 1927–1932, careful consideration was given to the study and application of the original method of Sauerbruch. In about 50 per cent of the cases phrenicectomy preceded thoracoplasty. The operations were very extensive with the removal of a great number of ribs. Only exceptionally was any portion of the lung allowed to remain intact. In resecting the rib an attempt

was always made to go as far as possible anteriorly, but on the other hand disarticulations were infrequent, nor were many transverse processes removed. The thoracoplasty was used mostly in cases of unilateral apical lesions with retractile tendency.

In the second period, 1932–1935, for the massive collapse of the involved side was substituted a more selective attempt to remove supporting structures. On the whole, it may be said that a smaller number of ribs were removed, but larger sections. In 1932, for the first time the first rib was disarticulated and removed in its entirety. The indications for thoracoplasty were interpreted more liberally, this accounting for somewhat greater mortality. In the surviving cases, the percentage of favorable results was higher than in the preceding four years.

In spite of more selective removal of supporting structures, one was still impressed by what appeared to be an uncalled-for mutilation of the thorax from both the anatomical and physiological point of view for what was frequently but a small lesion. The period from 1935 on was devoted to attempts to limit the procedure to the portion of the thoracic wall directly supporting the involved parenchyma.

It is too early to draw the final conclusion from our attempts from 1935 on, but it is well to note that the mortality rate has markedly diminished and in spite of more generous interpretation of indication and less extensive removal of supporting structures the evidence of excellent results is higher.

In the evaluation of results we adopted the following classification:

A: Excellent results: Perfect collapse of the involved area. Marked diminution of sputum or no expectoration. Absence of acid-fast bacilli on several consecutive examinations. Physical examination in these cases reveals no or dry râles, no functional respiratory embarrassment or circulatory trouble, absence of fever and satisfactory physical condition which allows the patient to pursue his activities.

B: Good palliation: The collapse is satisfactory. The lesion has markedly diminished but is not entirely collapsed. No evidence of spread. The laboratory examination reveals markedly diminished expectoration which may occasionally contain acid-fast bacilli. Temperature normal. Some gain in weight, but physical condition not satisfactory enough to permit returning to "normal" life.

C: Unsatisfactory results: The condition progressive as determined by X-ray and physical examination. Collapse inadequate. Fever. Acid-fast bacilli in the sputum which is not markedly diminished in quantity.

D: Death.

In table 1 we give the results during the three periods as well as the sum total of results. In summarizing the type of lesions it is interesting to note that: 3 per cent were small subclavicular cavities; 37 per cent were retroclavicular cavities; 25 per cent were subclavicular cavities in the cleido-parietal angle; 29 per cent were internal subclavicular cavities; 6 per cent only were diffuse multiple cavitations.

The operations were carried out for the greater part on women, 60 per cent being women. It is interesting to note that the left side involvement was more frequent in women than in men, 55 per cent of the left side being involve in women to 45 per cent in men. The proportion of cures in reference to the side is also noteworthy. In men, 26 per

TABLE 1

RESULTS	1927–1932		1933–1935		1935–1937	
A	93	44%	86	47%	35	37%
B	45	22%	39	21%	33	36%
C	32	15%	20	11%	13	14%
D	40	19%	36	21%	12	13%
Total	210	100%	181	100%	93	100%
Successful	138	66%	125	68%	68	73%
Unsuccessful	72	34%	56	32%	25	27%

Summary of results on 484 patients

A: 214	44%
B: 117	24%
C: 65	14%
D: 88	18%

cent of cures are obtained on the right to 30 per cent on the left, whereas in women 38 per cent of cures are obtained on the right to 42 per cent on the left. The operations were performed on individuals from the age of seventeen to fifty; we have but three cases where thoracoplasty was carried out on individuals below the age of seventeen.

SUMMARY

This report deals primarily with the experiences of French clinics since 1927. Altogether more than 700 thoracoplasties were performed, of which 484 are available for statistical purposes. They represent three distinct periods of technical endeavors carried out under the same direction.

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TUBERCULOSIS OF TONSILS[1,2]

A Study of 107 Patients following Removal of Tuberculous Tonsils

H. M. POLLARD AND A. B. COMBS

Even before the isolation of the tubercle bacillus, it had been suggested that tuberculous tonsils might serve as a source of spread of the disease throughout the body. Graber (1) in 1904, working on the lymphatic drainage of the tonsils in dogs, showed that three weeks following the injection of Chinese ink into the tonsils the dye could be traced into the deep cervical lymphatics and from there directly to the apical pleura and even into the parenchyma of the lung. Van Zwaluwenburg and Grabfield (2), in 1921, X-rayed 16 people with proved tuberculosis of the tonsils and found a "pleural cap" which they described as a clear line, usually seen along the inner surface of the second rib and separated from it by a clear space of 3 to 4 mm. They compared this result with 27 cases whose tonsils were not tuberculous and only three had pleural caps. Consequently they believed that a pleural cap was of a tuberculous nature resulting from downward extension of the infection from the cervical lymphatics after its entry through the lymphoid tissues of Waldeyer's ring.

Numerous other investigators, including Orth (3), Baumgarten (4), Dmochowski (5), Koplik (6), Wood (7), White (8), and others, have reported that a tuberculous infection may extend from the tonsil to the cervical lymphatics and even to the apical pleura.

It is conceivable that the mechanical manipulation necessary in surgically removing a tuberculous tonsil or adenoid may allow the entrance of the tubercle bacillus into the blood or lymphatic system and may result in extension of the disease elsewhere. The reports in the literature on the possibility of a nontuberculous bacteraemia following tonsillectomy are somewhat at variance. Southworth and Flake (9), in the most recent article on this subject, report on 22 patients on whom tonsillec-

[1] Presented at a session of the Clinical Section at the 34th annual meeting of the National Tuberculosis Association, Los Angeles, California, June 22, 1938.

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tomy was performed and from whom preoperative and postoperative blood cultures were taken; bacteraemia did not occur in any significant number of cases after tonsillectomy.

Very few follow-up studies have been conducted to demonstrate whether or not tuberculosis actually does spread following surgical removal of a tonsil or adenoid containing tubercles in a patient considered free of tuberculosis at the time of operation. With the hopes of obtaining some information on this subject at the Univerity Hospital, we have conducted such a follow-up study on 107 patients who, between the years 1925 and 1936, had their tonsils, adenoids, or both removed. The tissues on subsequent microscopical section showed the presence of tubercles.

McCready and Crowe (10) reported a follow-up study on 50 such patients in 1924 and found that tuberculosis of the cervical lymph nodes developed in 2 patients in the postoperative period; tuberculosis of the mediastinal lymph nodes developed in 3 with a normal preoperative chest roentgenogram; pulmonary tuberculosis developed in 5; and bone and joint tuberculosis appeared in 2. Six of 22 patients in whom no tuberculosis was suspected at the time of operation were still showing by X-ray progressive lesions in the chest at the end of their follow-up period of five years. In spite of these findings their conclusion is that a tuberculous infection of the tonsils or adenoids is of but little significance and might best be ignored. Leubner (11), in 1937, reports that a patient developed a serous tuberculous pleurisy following tonsillectomy and that the tonsils on microscopical section showed tuberculous alterations.

The entire group of 107 cases consisted of 53 males and 54 females, with an average age of 18.4 years and a range from three to fifty-seven. Each of these patients received a thorough physical examination prior to operation, and the operation was performed by a member of the otolaryngological staff. The tissue was routinely sectioned and examined microscopically by some member of the Department of Pathology and the results were reported according to Weller's (12) classification. He divides the tuberculous lesions of the tonsils into four groups as follows: (*1*) focal crypt infection which he considers to be due to an air-borne infection; (*2*) ulcerative lupus-like lesions (none of which are included in this series); (*3*) diffuse miliary tuberculosis in which the tubercles occur in the follicles and germ centres and must be due to a haematogenous dissemination; (*4*) mixed type, which is a combination of the crypt infection and the diffuse miliary type.

Our follow-up information was obtained from the patient's own record at the University Hospital, and by questionnaires and letters sent out by the Social Service Department; they gathered all available reports which the Michigan State Tuberculosis Society had obtained in school surveys and check-up examinations on these patients in clinics. When the patient had visited a physician since leaving here or had been in a sanatorium or hospital, the available records were likewise obtained. Therefore in speaking of the follow-up we shall refer to information obtained directly from the patient as that obtained "by letter." The chest X-ray films were in most instances made at the University Hospital, but a few are reports sent us by other hospitals or the Michigan State Tuberculosis Society.

Ninety of the 107 patients received a chest X-ray film either shortly before or shortly after the operation. Sixty-three of the entire group were followed beyond the immediate postoperative period, and these were followed by letter, X-ray or both, for an average time of 4.4 years after the operation.

SUMMARY OF POSTOPERATIVE OBSERVATIONS

Tuberculosis of the lung: Of the 107 patients with tuberculosis of the tonsils or adenoids, there were 15 (cases 4 to 18 inclusive) who had pulmonary tuberculosis at the time of the operation, and 3 (cases 1, 2 and 3) who developed it at some time subsequent to the operation. These three are summarized below.

Case 1: (T. G., no. 130281) A white female, aged 12, had Pott's disease at the time of operation May 4, 1931. Miliary tubercles were found in the adenoids following operation, though the tonsils were reported negative. Chest X-ray films were negative prior to operation and four months postoperatively, at which time the patient was admitted to a sanatorium for treatment of her Pott's disease. Periodic chest films thereafter remained clear for two years before the development of a minimal lesion. During this time the spine had shown improvement.

Case 2: (E. F., no. 157659) A white female, aged 8, had tuberculosis of the left hip at the time of the operation, April 11, 1928. The pathologist reported cryptic miliary tuberculosis of one tonsil. Three chest X-ray films prior to operation had all been negative and one X-ray film eight months postoperatively was negative. The next check-up was not until two and one-half years following operation and at that time a minimal lesion was diagnosed in the

film. She was discharged as "arrested" from a sanatorium in May, 1933, five years after operation.

Case 3: (C. W., no. 247589) A white male, aged 21, was hospitalized for unresolved pneumonia from March to July, 1933. A tonsillectomy was performed on November 28, 1933, and the pathology report described a "haematogenous tuberculous infection" in one tonsil. One month postoperatively the patient developed enlarged cervical lymph nodes which were finally incised and drained in June, 1934. A culture of tubercle bacilli was obtained from this material. Chest X-ray films at the time of operation and again six months later did not show any evidence of tuberculosis. However, fourteen months postoperatively a diagnosis of a minimal tuberculous lesion was made by X-ray.

Of the 15 patients mentioned above who had pulmonary tuberculosis at the time of operation, the diagnosis was known preoperatively in only 6 (13 to 18 inclusive). The other 9 cases (4 to 12 inclusive) are significant in that pulmonary tuberculosis had not been suspected from the history or physical examination at the time of operation and the X-ray examination was indicated only after the discovery of tubercles in the tonsillar tissue. Two were minimal, 4 were moderately advanced and 3 were far advanced. Two of the 9 (6 and 8) eventually died of their tuberculosis, one after five and one-half years and the other after nine years. Three cases (7, 11 and 12) were still in a sanatorium receiving treatment for their pulmonary lesion, six years, five years and four years respectively following operation. One case (4) was showing a progressive lesion eighteen months after operation, and six years postoperatively was still having pulmonary symptoms. Two cases (5 and 7) had become apparently arrested, four years and five years respectively after operation. One patient (10) was not followed after the diagnostic X-ray film was taken.

Microscopical examination of the tonsils in the 9 cases (4 to 12 inclusive) showed a cryptogenic infection in five, and a blood-stream infection in four. The 6 patients (13 to 18 inclusive) who had known pulmonary tuberculosis at the time of operation all showed miliary tubercles in the tissue examined. None of the chest X-ray films in the above groups showed a miliary type of involvement.

Tuberculosis of the mediastinal lymph nodes: Of the 107 cases there were 6 with tuberculosis of the mediastinal lymph nodes, 3 of whom were diag-

nosed roentgenologically shortly before operation, and 3 were diagnosed shortly after operation by a chest X-ray film which was taken due to the tubercles reported in the tonsils. These cases are summarized as follows:

Case 19: (H. H., no. 144966) This white female, aged 6, was diagnosed "hilum tuberculosis" by the roentgenologist on June 1, 1926, and the operation was performed on September 10, 1926. At the time of operation she also presented enlarged cervical nodes which had been draining one and one-half years. The pathologist reported tubercles in both tonsils, "cryptogenic infection." She was admitted to a sanatorium on October 26, 1927 and was discharged from there as "arrested" on June 13, 1933.

Case 20: (A. M., no. 152682) White male, age 14. The patient did not have a preoperative chest roentgenogram, but a complete physical examination was negative at the time of operation September 7, 1926. A chest X-ray film taken a few days following operation showed "lymphoid infection" which was considered nonspecific at that time by the roentgenologist. Subsequent X-ray films three and one-half years and four and one-half years following operation were all reported as negative. The pathologist reported a "blood-borne tuberculous infection" in one tonsil and in the adenoids. A letter from the patient eleven years after operation stated that she was in good health.

Case 21: (J. O., no. 174760) This white male, aged 5, was operated July 29, 1927. A preoperative chest X-ray film showed "hilar enlargement" and another taken three days after operation was reported as "entirely negative." The pathologist found miliary tubercles around the tonsillar crypts. This patient wrote ten years following his operation that he was in good health.

Case 22: (N. T., no. 192392) This white female, aged 43, had had tuberculous cervical lymph nodes removed June 5, 1930 and a tonsillectomy on July 24, 1930. Here again a preoperative chest X-ray film showed "hilar enlargement" and a check-up film taken five days after operation was reported as "entirely negative." The pathologists found multiple tubercles in the tonsils located around the crypts. This patient died outside of the hospital in September, 1933, and the cause of death listed on the death certificate was "diabetes, intestinal obstruction and gall stones."

Case 23: (B. S., no. 216172) This white female, aged 10, was operated May 9, 1929. There was no preoperative chest X-ray film taken, but one four days postoperatively showed "increase in the hilum shadow." Another X-ray

film taken eight days postoperatively showed "no change." The pathologist reported the presence of several miliary tubercles in the tonsils. Unfortunately there is no further follow-up information available.

Case 24: (B. R., no 257279) This colored female, aged 6, was operated January 29, 1931. There was no preoperative chest X-ray film, but one taken thirteen days following operation showed "enlarged hilar lymph nodes" and a parenchymal lesion at the right base which was considered pneumonic by both the roentgenologist and the clinician. The pathologist reported the presence of miliary tubercles about the crypts of one tonsil. All physical signs in the chest disappeared and the patient was discharged in good condition from the hospital 28 days postoperatively. No further information is available.

There were no cases therefore that were proved to have actually developed mediastinal involvement or other evidence of tuberculosis following operation. The period of observation for this group averaged six years. Four cases showed a cryptogenic type of infection pathologically and two a haematogenous type of infection.

Tuberculosis of the cervical lymph nodes: Of the 107 cases there were 12 with tuberculous cervical adenitis, 11 of whom were known at the time of operation and one following operation. This one developed pulmonary tuberculosis and is case 3 which is summarized under *Tuberculosis of the lung.*

Case 26: (M. W., no. 166581) This white female, aged 29, presented several cervical nodes the size of a walnut at the time of the operation May 5, 1927. These nodes were considered tuberculous by examination. Two months after operation they had enlarged to the size of an egg and at that time they were excised. The pathologist found tubercles of the cryptogenic type in both tonsils, and the excised lymph nodes likewise showed tubercles. A preoperative chest X-ray film was negative but none was taken postoperatively. This patient replied to our questionnaire ten years after operation and reported that she was in good health and asymptomatic.

Case 29: (I. H., no. 177762) This white male, aged 11, presented enlarged cervical nodes which were considered tuberculous by the clinician at the time of operation August 24, 1927. The pathologist found miliary tubercles in the tonsillar crypts. The lymph nodes increased in size following operation, and four months postoperatively they were incised and drained. A biopsy of the

material removed showed a mixed tuberculous and pyogenic infection. The chest X-ray film five months after operation was entirely negative. No further information is available.

Case 32: (R. Z., no. 147324) At the time of operation, May 21, 1928, this white male, aged 14, had enlarged cervical lymph nodes which were considered tuberculous. He likewise had tuberculosis of the left ankle and left wrist and this diagnosis was made preoperatively by a biopsy. A preoperative chest X-ray film was negative and following operation the pathologist reported "active tuberculosis" of the cryptogenic type in the tonsils. The cervical lymph nodes began to enlarge in 1931 and several months later broke down and drained. The last chest X-ray film three years after operation was still negative, and physical examination four years after operation revealed that the patient was free of signs and symptoms of active tuberculosis.

Two cases (22 and 27) of this group of 12 with tuberculous cervical adenitis had their cervical lymph nodes removed six weeks prior to the operation and the diagnosis was confirmed pathologically. The remaining 6 cases, however, (19, 20, 25, 28, 30 and 31) were diagnosed entirely by the clinical picture. With the exception of case 3, this group was followed for an average of 4.7 years and each was in good health at the end of that period. Pathologically, 4 cases showed a haematogenous infection and 8 showed the cryptogenic form.

Tuberculosis of the bones and joints: Of the 107 patients with tuberculosis of the tonsils or adenoids, 8 had bone and joint tuberculosis. In 7 of this group the diagnosis of the orthopedic complication had been made prior to tonsillectomy and in only one case did a bone and joint lesion develop subsequent to the tonsillectomy. This case is described as follows:

Case 36: (A. S., no. 224349) This white female, aged 3, had had cervical lymph nodes removed before entering this hospital, and from the information available these nodes were probably tuberculous. A preoperative chest X-ray film was negative and the tonsillectomy was performed November 20, 1929. The pathologist reported "miliary tuberculosis of the tonsils and adenoids, haematogenous infection." One and one-half years following the tonsillectomy this patient developed symptoms of Pott's disease and the diagnosis was confirmed by clinical and X-ray examination. The spine was fused sixteen months later. Chest X-ray films were negative until three and one-half years

following removal of the tonsils. The questionnaire eight years following removal stated that she was still having symptoms referable to the spine only.

Two of the 7 remaining cases developed pulmonary tuberculosis and are cases 1 and 2, reported in the section on *Tuberculosis of the lung*. As noted, their condition was considered to be "improving" after six years in case 1, and "arrested" after five years in case 2. A third patient, case 32, had tuberculous cervical adenitis and is described under that section. This patient was considered "arrested" four years after the tonsillectomy. The other 4 patients, 33, 34, 35 and 37, were followed for five years, ten years, nine years, and three years, respectively, and all showed arrested lesions at the end of that observation period.

In summarizing the pathological lesions in the tonsils of these 8 cases, we found a haematogenous miliary tuberculous infection in 5, and a cryptogenic infection in 3.

Tuberculosis of the tonsils and adenoids only: There are 37 cases accounted for in the various groups above. This leaves 70 of the total of 107 cases with no tuberculous lesion discovered at the time of operation other than in the tonsils or adenoids. None of this group of 70 had any clinical evidence of tuberculosis at the time of the tonsillectomy and the discovery of tuberculosis in the tonsils or adenoids; none is known to have developed other tuberculosis or ill health. Six of the 70, however, had no X-ray film of the chest at any time and the patients cannot be located.

Twenty-two of the 70 had negative chest X-ray films at the time of the tonsillectomy, but their postoperative record is not known.

Twenty-three of the 70 also had negative chest X-ray films at the time of the operation, and subsequent roentgenological follow-up for an average period of four years remained negative. Letters over an average postoperative period of six years reported them all in good health.

Although 19 of the 70 had negative roentgenograms at the time of operation they had no subsequent ones. These 19 have reported by letter that they are in good health on an average of six years later.

Analyzing the type of tuberculous lesion present in this group of 70 cases, there were 37 with a cryptogenic type of infection, 31 with miliary or haematogenous infection and 2 with a combination of both forms.

DECREASING INCIDENCE

Some of the more recent reports on incidence of tuberculous infection of the tonsils are as follows:

AUTHOR	SOURCE OF INFORMATION	YEAR OF REPORT	PERCENTAGE INCIDENCE	NUMBER OF CASES
Mullin (13)	Colorado Springs	1923	4.25	400
McCready and Crowe (10)	Baltimore	1924	4.18	3,260
Howarth (14)	London	1924	5.0	100
Cornell (19)	Isthmian Canal Zone	1927	1.49	2,336
Scarff and Whitby (15)	London	1928	2.0	
Wilkinson (16)	Rochester, Minn.	1929	0.5	10,000
Rössner (17)	Frankfurt-am-Main	1933	1.01	296
Newhart, Cohen and Van Winkle (18)	Glen Lake Sanatorium	1934	1.0	100

Comparative figures on incidence are available from the Pathology Laboratories of the University of Michigan where Weller (12) reviewed 8,697 unselected tonsils submitted for histological examination and found tuberculous infection involving 3.0 per cent in 1917 and 2.7 per cent in 1920. Magee (20) followed this with an analysis of 6,280 cases submitted to the same laboratory during the years 1933–1935 and reported an incidence of 0.44 per cent of tuberculous infection. Although the material received in Weller's Laboratory came from the entire state of Michigan, we find that the same diminishing incidence of infection is reflected in the cases operated at the University Hospital. The records here show that from 1925 through 1936 there were slightly over 23,000 cases who had tonsils, adenoids, or both removed. In 1926, 15 cases, representing 0.94 per cent of those operated, showed tuberculous infection. The incidence abruptly diminishes in 1930 and in 1936 only 4 cases were detected, an incidence of 0.26 per cent. The average incidence for the period was 0.44 per cent.

Park and Krumwiede (21) in 1910 reported that the majority of the tuberculous lymph nodes of the neck in children are due to an infection with the bovine bacillus. Mitchell in 1917 differentiated the type of tubercle bacilli in a group of faucial tonsils removed from children and concluded that 75 per cent of the tuberculosis of faucial tonsils in children under the age of ten is due to drinking milk from tuberculous cows. McCready and Crowe, 1924, (10), and Vlasto, 1931, (22), concur in this viewpoint.

In attempting to obtain some explanation for the diminishing inci-

dence, we ascertained (23) that Michigan began tuberculin testing cattle in 1921 and at that time approximately 4.5 per cent of the cattle were infected. Michigan became a "fully modified accredited area" during August, 1930, and incidentally was the third state in the Union to reach such a status. At present the general percentage of infection based upon six or seven hundred thousand individual cattle tests is well below 0.2 per cent. Although it is not known that all our patients were raised in Michigan, in view of the average age (18.4) it is only reasonable to assume that the majority are natives of Michigan, and have probably been affected by the diminishing incidence of tuberculosis in cattle.

Another factor which possibly has altered the incidence here may be purely a local one, since the state laws on the care of the indigent sick have varied the age group on whom we are now doing tonsillectomies in this institution.

SUMMARY

In all, there were 3 cases that developed active pulmonary tuberculosis in the postoperative period of observation, one that developed cervical lymph node tuberculosis, and one that developed tuberculosis of the spine. Nine cases with pulmonary tuberculosis at the time of operation were not diagnosed until the pathologist had submitted a report describing tubercles in the tonsils. This report prompted the taking of the diagnostic chest X-ray films. Three cases were found to have tuberculosis of the mediastinal lymph nodes.

Twenty cases with tuberculosis other than the tonsils and adenoids at the time of operation did not subsequently develop an additional lesion.

Seventy cases with no other tuberculosis at the time of operation did not develop it or any ill health subsequently.

Of the 107 cases, the pathologist reported the presence of tubercles located near the crypts in 56 cases. There were tubercles in the germinal centres indicating a haematogenous infection in 51 cases.

The incidence of tuberculous infection of the tonsils or adenoids has shown an actual decrease in the state of Michigan. This bears some correlation in time with the control of tuberculosis in cattle in this state.

CONCLUSIONS

1. A histological examination should be made of the tonsil and adenoid tissue removed at operation.
2. Every patient whose tonsils or adenoids are discovered to contain

tubercles should be carefully examined for tuberculosis elsewhere, and he should have a chest X-ray film.

3. Patients with tuberculous tonsils who have a negative chest X-ray film and are free of any other extrapulmonary tuberculosis at the time of operation, rarely develop it.

4. Patients with tuberculous tonsils and evidence of tuberculosis elsewhere should be carefully observed postoperatively for further spread of the disease.

The authors wish to express their sincere appreciation to Dr. John B. Barnwell for his kind assistance and criticism offered throughout the preparation and writing of this report.

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TREATMENT OF TUBERCULOUS TRACHEOBRONCHITIS[1]

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During the past six years there have been reports in increasing numbers of tuberculous tracheobronchial complications in pulmonary tuberculosis. It is now definitely established that tuberculous involvement, particularly of the larger air passages, is a fairly common occurrence in the presence of tuberculous pulmonary disease. Eloesser (1), McConkey and Greenberg (2), Ballon (3), Crimm and Strayer (4), Epstein and Ornstein (5), Myerson (6), Samson (7), Barnwell, Littig and Culp (8) have reported on the incidence, types and symtomatology of this complication, almost all within the past four years.

The mode of infection is still debatable, but the work of Reichle and Frost (9) on autopsy material leads to the view that the most frequent avenue by which the bronchial mucosa becomes infected is along the bronchial mucous glands which extend from the bronchial mucosa to the peribronchial alveoli, lymphatics and lymph nodes. Tuberculosis seems to show a predilection for these glands which form a portal of entry past the barriers of cartilage, muscle and elastic tissue. These authors feel that, though direct implantation from sputum can occur, it is rare because of the protective action of cilia, mucus and bronchial peristalsis.

From recent reports, notably those based on autopsy study, one would conclude that these lesions occur chiefly as a complication of far advanced pulmonary tuberculosis. Several of our cases developed fairly extensive tracheobronchial lesions while the parenchymal involvement was moderate in extent and even showing evidences of healing.

It is undoubtedly true that some of these lesions heal spontaneously, but it is also true that many patients with this complication fail rapidly unless the bronchial involvement is recognized and treated. During the past twenty months we have observed and treated eight patients with tuberculous lesions of the tracheobronchial tree. Prior to the commencement of treatment the bronchial symptoms were at a standstill or were increasing. One patient's symptoms were unimproved over a period of six months previous to the beginning of treatment.

[1] From Devitt's Camp for the Treatment of Tuberculosis, Allenwood, Pennsylvania.

Another had definite symptoms of a bronchial lesion for two years before specific treatment was begun. The reports of Samson, Barnwell, Littig and Bugher (10), and of Bugher, Littig and Culp (11) indicate clearly that tuberculous patients who develop bronchial lesions have a poor prognosis unless treated.

CLINICAL SYMPTOMS

Wheeze is the most frequent and most reliable symptom of a tuberculous tracheobronchial lesion. The wheeze indicative of such lesions is not transitory, though varying in intensity, but persists over days, weeks or months. The wheeze persists after expectoration, is loudest over the site of the lesion, and often transmits marked vibrations to the palpating hand. It is usually most evident in the parasternal regions. The wheeze may only be produced on exertion or forced expiration, and thus may be missed during quiet breathing. In eliciting these signs it is important to request that the patient take a deep breath and then exhale forcibly, while the stethoscope is applied to the parasternal regions. If pneumothorax is present the wheeze may sometimes best be heard by placing the stethoscope over the suprasternal notch as the sounds are transmitted up the trachea. In arriving at a clinical diagnosis it is also important to make repeated daily stethoscopic examinations, particularly after the patient has expectorated as completely as possible.

Dyspnoea is often associated with the wheezing, and should be a suspicious symptom when out of proportion to the patient's other findings. A sense of obstruction often accompanies the dyspnoea.

Positive sputum persisting after obtaining good collapse of the diseased area always should suggest the presence of a tracheobronchial lesion, particularly when accompanied by periods of fever and sputum block with resulting marked variations in amount of expectoration. Difficulty in raising sputum is suggestive.

Continuous or intermittent atelectasis of one or more lobes is a very definite indication of bronchial obstruction, and therefore of a bronchial lesion. During the periods of atelectasis the wheeze may disappear because of the complete bronchial block, and recur when a partial lumen is again established.

METHOD OF TREATMENT

In the treatment of these lesions we have been using the high frequency electrocoagulating current applied by means of the Kernan[2]

[2] This electrode is manufactured by George P. Pilling & Son, Philadelphia, Pennsylvania.

electrode through either a 5, 6 or 7 mm. bronchoscope. We feel the strength of the current used should be of low intensity so as to minimize the possibility of producing necrosis of cartilage in the bronchial wall. Accurate standardization of current is probably not important because the effectiveness of coagulation at a given point for a given strength will vary, depending on the amount of mucus or other exudate between the electrode and the diseased tissues. We keep the current control at its lowest point unless a mass of tissue projecting into the bronchial lumen is to be destroyed. The length of time that the electrode is applied at any one point varies from one to five seconds. Generally speaking, we try to avoid producing coagulation deeper than 1 mm. Our purpose is not to attempt to destroy all of the tuberculous tissue present, but to stimulate the reparative processes of nature.

Cauterization of tuberculous laryngeal lesions has been an accepted form of treatment for many years. Electrocoagulation has the same physiological effect as the actual cautery, namely, the production of a burn. This is beneficial probably because it induces hyperaemia and hastens fibrosis. It should be kept clearly in mind that we are not endeavoring to destroy all the tuberculous tissue present, but merely to hasten cicatrization of the lesion by stimulation of the natural tissue response.

It seems apparent that these lesions spread by continuity along the submucosa. They seem to originate in most cases in the bronchus draining the affected lobe and spread outward into the next larger bronchus. Since we have available a means of inducing healing in small ulcers it is important that the diagnosis be made early and treatment instituted before the ulcer has had time to involve the entire circumference of a major bronchus. It is obvious that there will be less scarring and contraction from healing of a small ulcer than there will be from healing of a large one. If treatments are gently carried out and normal mucosa is not burned or traumatized, we do not think there will be any more cicatricial stenosis than would have developed from spontaneous healing if that should occur. In our experience, mechanical dilatation of fibrous strictures has not been effective except for very temporary relief of sputum retention. Cicatricial stenosis of marked degree is still a serious problem for which lobectomy may eventually prove to be the solution. Cautery excision of these severe stenoses involves a very real danger of perforation of the bronchial wall.

RESULTS OF TREATMENT

Eight patients with tuberculous tracheobronchial lesions have been treated over a period of twenty months by electrocoagulation current of weak intensity. Treatments were given at intervals of two to four weeks. No harmful effects were noted as a result of bronchoscopic treatment and in each case the tracheobronchial lesions showed a consistent tendency to heal. A total of eighty-four treatments were given. There were no laryngeal complications and no spread of the parenchymal lesions was observed.

Five patients are clinically well. Two of these patients show complete healing of their tracheobronchial lesions but still show occasional positive sputum. Two patients are improving satisfactorily under treatment. Treatments were discontinued in the other case because of the patient's extreme debility and emaciation. The patient longest under treatment has had no recurrence of positive sputum or wheeze in the year following healing of her tracheobronchial lesion.

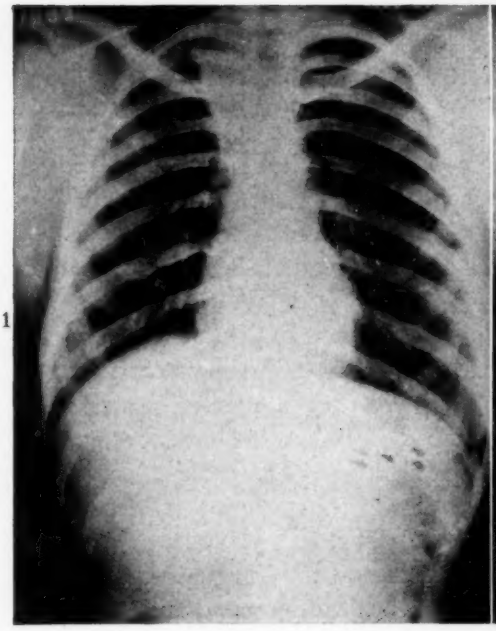
The series is small but the results of treatment are in agreement with those of a much larger series reported by Warren, Hammond and Tuttle (12). In large degree we have followed the treatment method of these authors, and we believe great credit is due them for advances in the management of a complication often presenting an otherwise gloomy prognosis.

The following case histories will illustrate the symptoms and progress of patients having tracheobronchial lesions.

Case Reports

Case 1: C. Y., female, age 26, admitted February 2, 1936. Diagnosis of pulmonary tuberculosis suspected five months before, but not definite until one month before admission. There was history of slight cough and intermittent wheezing over past six months. On admission the sputum was positive for tubercle bacilli, and the X-ray film of the chest indicated an atelectasis of the right upper lobe, which was not present on films taken three weeks previously. No wheeze was present. Serial roentgenograms at two-week intervals showed the presence of atelectasis until April 21, 1936, when the films showed sudden and complete reëxpansion of the right upper lobe. At this time the wheeze reappeared, loud enough to be heard easily without a stethoscope. It was loudest in the right parasternal region and transmitted marked vibrations to the palpating hand. The wheeze was often absent on quiet breathing, but could almost always be produced on forced expiration. Although there ap-

FIG. 1



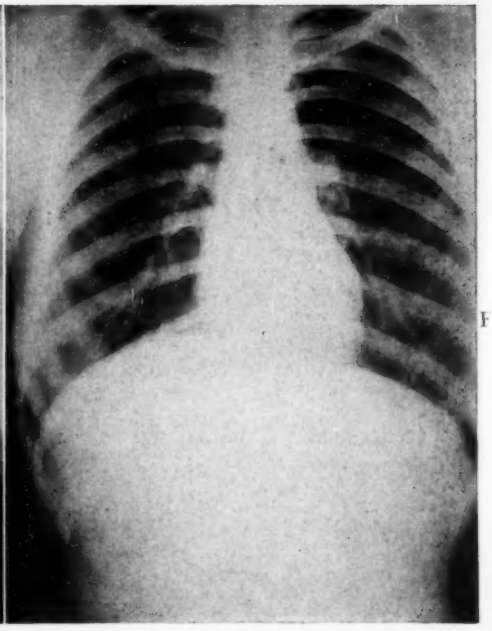
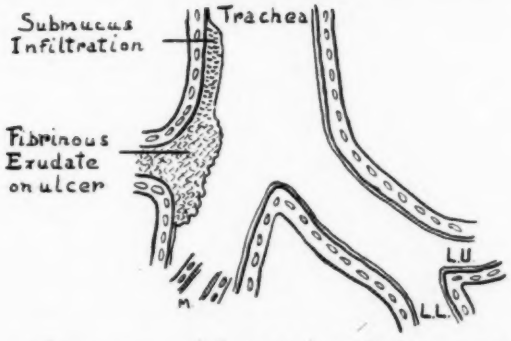


FIG. 2



Parenchymal lesion located in right upper lobe.

FIG. 3

FIG. 1. Case 1. February 3, 1936. Triangular density indicating atelectasis of right upper lobe. Sputum positive for tubercle bacilli. No wheezing.

FIG. 2. Case 1. April 21, 1936. Atelectasis has disappeared. Positive sputum continues and wheezing has returned.

FIG. 3. Case 1. August 11, 1936. Bronchoscopic appearance.

peared but a small amount of infiltration in the expanded upper lobe and no cavity was demonstrated, the sputum was persistently positive for tubercle bacilli.

Right pneumothorax was induced on April 22, 1936, and a complete collapse of the upper lobe obtained. The wheezing and positive sputum continued, however, and on August 11 a bronchoscopic examination was made by Dr. F. W. Davison, the report of which is as follows: "There is a gray, slightly nodular raised plaque of tissue on the right posterolateral wall of the trachea, beginning about one inch above the carina. The lower portion of this area of thickened mucosa around the orifice of the right upper lobe is ulcerated, and covered with tough adherent fibrinous exudate." This area was treated by electrocoagulation through the bronchoscope at two-week intervals over a period of months until February 4, 1937. At this time the bronchoscopic report was as follows: "The endobronchial lesion has healed completely. There is only a small amount of scarring at the site of the former lesions, and only a moderate reduction of the lumen in the right main bronchus. The normal location of the right upper lobe bronchus is covered by a sheet of smooth white scar tissue."

During the bronchoscopic treatments there was a progressive decrease in the expectoration and a gradual lessening of the wheeze. The sputum became negative for tubercle bacilli by January, 1937, and has remained negative to the present. Right pneumothorax has been maintained to the present, although it is believed that the right upper lobe will remain atelectatic because of the stenosis in its bronchus. The patient has been free from symptoms to the present, approximately one year following the healing of her tracheobronchial lesion.

Case 2: E. E., female, age 24, admitted June 6, 1934, with a history of pulmonary tuberculosis since May, 1933. The lesion on admission involved chiefly the left upper lobe, although previously the left lower lobe had shown the greatest disease. The sputum was positive for tubercle bacilli. Left pneumothorax was induced October 10, 1934. The sputum became negative within a month, and the clinical course of the patient was progressively favorable. She left the sanatorium in May, 1935, continuing pneumothorax at home.

She continued in good health until April, 1937, when bronchial wheezing began, and continued in varying degree. The sputum reappeared, and was tenacious and difficult to raise. Tubercle bacilli were again present over a period of several months. She was readmitted to the sanatorium July 31, 1937, complaining of constant wheezing over the left chest, and of difficulty in raising her sputum. She stated that a feeling of blocking persisted even after cough and expectoration. On physical examination, the wheeze seemed generalized over the left chest, and was not localized over one area. An X-ray film of the chest at this time showed no evidence of parenchymal involvement either in the partially collapsed left lung or in the contralateral lung. No visible source of positive sputum could be seen. A pneumonogram on August 10, 1937, re-

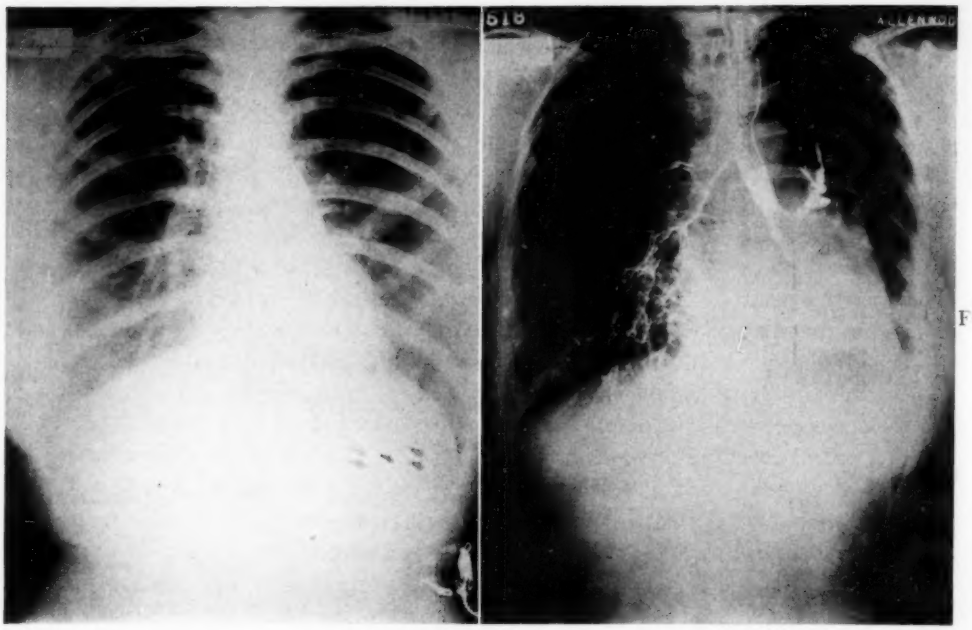
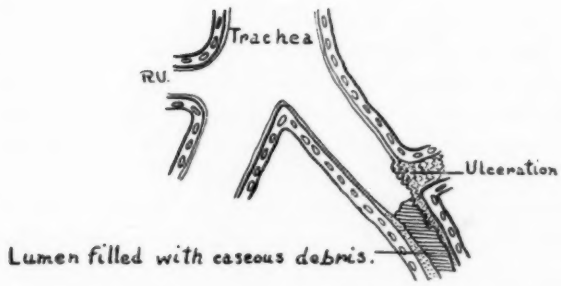


FIG. 5



Cavity previously present in left lower lobe.
Left lower lobe atalectatic at time of
first bronchoscopy.
Left pneumothorax.

FIG. 6

FIG. 4. Case 2. August 1, 1937. Left pneumothorax. No apparent parenchymal lesion, but marked wheezing and positive sputum.

FIG. 5. Case 2. August 10, 1937. Bronchogram showing partial stenosis of left upper lobe bronchus, and occlusion of left lower lobe bronchus.

FIG. 6. Case 2. August 16, 1937. Bronchoscopic findings.

vealed a partial stenosis of the left upper lobe bronchus, and complete obstruction of the left lower lobe bronchus. A bronchoscopic examination seemed indicated, and Doctor Davison's report is as follows: "The trachea and right main bronchus appeared normal. There is ulceration completely surrounding the orifice of the left upper lobe bronchus. The left lower lobe bronchus was completely filled with grayish white caseous exudate. This was cleaned out with an aspirator, but there was still a tough fibrinous exudate adherent to the anterolateral wall."

The ulcerated surfaces were treated with electrocoagulation at two-week intervals over a period of three months. At this time the bronchoscopist's report was: "The ulceration previously noted is now completely healed. The left upper lobe bronchus has a diameter of about 3 mm., and the left lower lobe bronchus has a diameter of about 2 mm. Both bronchi were empty, and no secretion could be seen when the patient coughed on request."

At the end of this interval under treatment, the patient's wheeze had disappeared, and there was very slight expectoration. This was negative for tubercle bacilli, and has remained so to date. The general condition of the patient is excellent, and she is now continuing her pneumothorax treatments without symptoms.

Case 3: A. W., female, age 29, admitted January 30, 1937, with history of pulmonary tuberculosis for previous five months. On admission there was X-ray evidence of active right upper lobe involvement, without demonstrable cavity. The sputum was positive for tubercle bacilli. Right pneumothorax was attempted, but no intrapleural space could be found. On bed-rest there was rapid clinical improvement, and progressive clearing of the right upper lobe lesion.

In March, 1937, intermittent wheezing was noted, localized over the right parasternal region, and reappeared two months later, with more severity. There were now periods of sputum block, and tubercle bacilli were more numerous in the sputum in spite of the improvement in the pulmonary lesion. The wheeze was more marked on forced expiration and there were easily palpable vibrations over the right upper lobe.

The report of the bronchoscopic examination on July 18, 1937, was as follows: "There is an ulcer on the right hand wall of the trachea which begins one-half inch above the carina and extends down to include the orifice of the right upper lobe bronchus. The ulcer is about one-quarter inch in width, and involves the whole circumference of the right upper lobe bronchus. The right upper lobe bronchus appeared to be almost completely occluded by yellow fibrinous exudate, and the surface of the ulcer was covered with yellow purulent exudate which could be removed with an aspirator. The right stem bronchus and left main bronchus appeared to be normal."

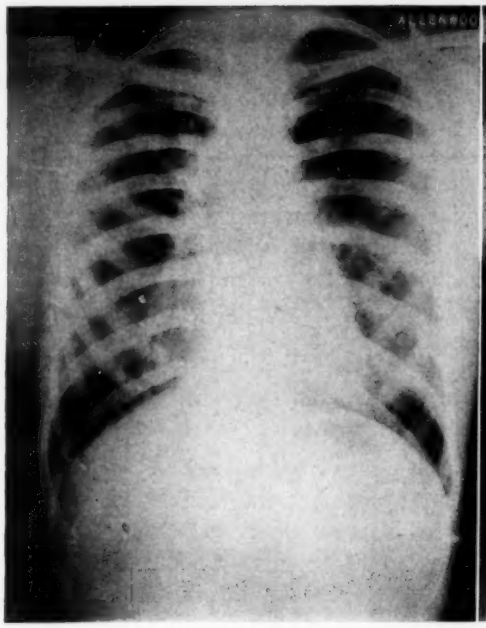


FIG. 7

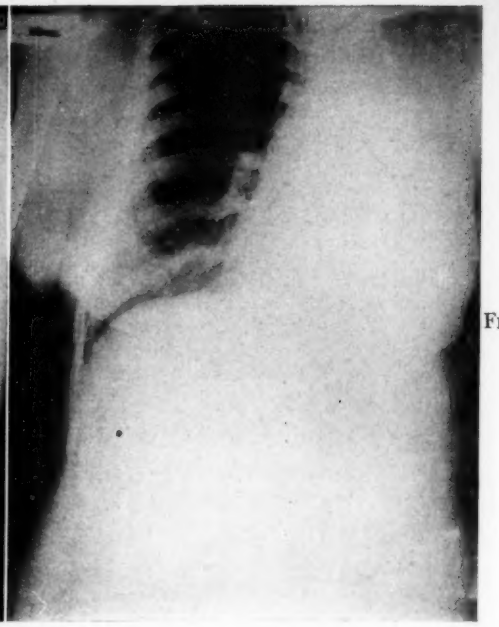
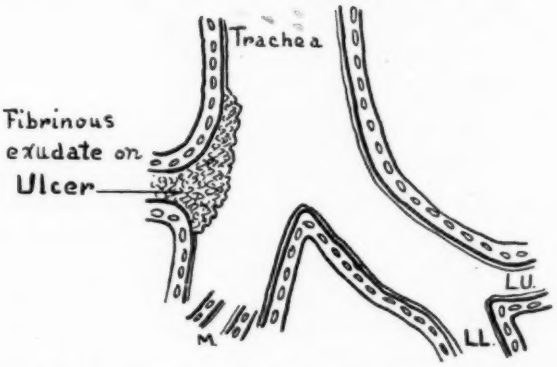
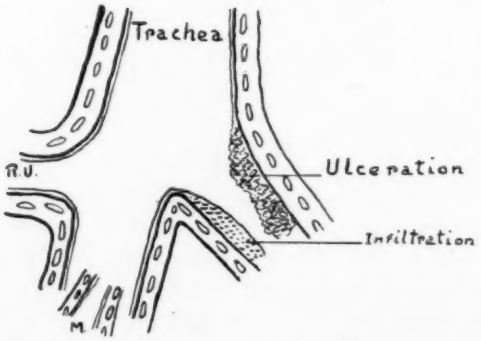


FIG. 9



Parenchymal lesion located in right upper lobe.

FIG. 8



Parenchymal lesion in left lower lobe.
Total left thoracoplasty.

FIG. 10

FIG. 7. Case 3. Moderately advanced right upper lobe lesion. No visible cavity. Marked wheezing and positive sputum.

FIG. 8. Case 3. Note extensive tracheobronchial lesion in comparison to small parenchymal involvement seen on X-ray. (See fig. 7.)

FIG. 9. Case 4. Positive sputum persisting after complete thoracoplasty.

FIG. 10. Case 4. Bronchoscopic appearance at first bronchoscopy nine months after completion of thoracoplasty.

A series of electrocoagulation treatments through the bronchoscope was carried out at two-week intervals over a period of months. The wheeze gradually disappeared, and the sputum was greatly reduced. On April 6, 1938, the bronchoscopic report was as follows: "The site of the former ulceration at the bottom of the trachea and around the orifice of the right upper lobe bronchus is now entirely healed. There is firm, white, scar tissue underneath the mucosa in this area, and no definite point can be found to mark the previous opening of the upper lobe bronchus. There is no excess mucus or other discharge in the bronchial tree at present." In spite of this there is still occasional small expectoration containing a few tubercle bacilli. This may be from the parenchyma, or from ulceration in a small branch of the upper lobe bronchus, beyond view of the bronchoscope.

Case 4: E. N., female, age 34, admitted March 10, 1935; treated for pulmonary tuberculosis at another institution for the previous eighteen months. Left pneumothorax was begun fourteen months ago, but had been abandoned. On admission, left pneumothorax was reinduced to combat an extensive infiltrative process most marked in the left lower lobe. Only a 30 per cent collapse could be obtained, because of extensive adhesions, and the sputum remained positive for tubercle bacilli. In June, 1935, there was noted an increasing wheeze over the left chest, markedly exaggerated during expiration, and accompanied by blocking and difficulty in raising sputum. There were prominent palpable vibrations during expiration over the left parasternal region. These symptoms continued with varying severity until the lung reëxpanded under pleural effusion in January, 1936. No further wheezing was noted, and the clinical course of the patient made other collapse measures advisable. A complete left thoracoplasty was performed during June and July, 1936, preceded by crushing the left phrenic nerve. In spite of an apparently efficient collapse, the sputum remained positive for tubercle bacilli over a period of six months.

A tuberculous tracheobronchial lesion was suspected, and the absence of wheeze explained by the complete collapse of the lung so that no air current existed. The patient refused bronchoscopy until March 13, 1937, when the bronchoscopic notes were as follows: "There are two small tuberculous ulcers on the trachea, two inches and one-half inch above the carina. The carina was much broader than normal, apparently due to thickening of the mucosa and submucosa. About one-half inch past the carina there was marked thickening of the left lateral wall of the left main bronchus, so that the lumen was almost completely occluded. This was superficially ulcerated, and there was considerable oozing. The right main bronchus was examined and found to be normal."

A series of bronchoscopic treatments were carried out at two-week intervals, with applications of electrocoagulation. On December 1, 1937, the bronchoscopic report was as follows: "The tracheobronchial mucosa appeared normal.

There was no excess mucus in the bronchial tree. The mucosa around the left main bronchus is smoothly healed. There is a funnel shaped stenosis of the left main bronchus so that an inch past the bifurcation the lumen of the left main bronchus is not more than 2 mm. in diameter."

The cough and expectoration decreased progressively after the beginning of bronchoscopic treatments, and the sputum became negative for tubercle bacilli in July, 1937, and has remained so, with few exceptions, to the present. The patient is now free from symptoms, though there occurs slight amount of clear expectoration from time to time.

CONCLUSIONS

1. In our observation patients with symptoms of tuberculous tracheobronchitis have failed to show improvement under ordinary methods of treatment, including collapse therapy.

2. Tracheobronchial lesions have shown a consistent tendency to heal in response to treatment by electrocoagulation.

3. No harmful effects attributable to bronchoscopy or electrocoagulation were noted.

We are greatly indebted to Dr. William Devitt for his advice and assistance in the management of these cases. We are also indebted to Dr. Christopher J. Stringer for his valuable suggestions.

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MYOCARDIAL TUBERCULOSIS[1]

A Cause of Congestive Heart Failure

E. LLOYD WILBUR

Congestive heart failure as a result of myocardial insufficiency is a frequent clinical entity. The basis of this syndrome is usually obvious; however, there is an occasional case in which the aetiology of the myocardial damage is obscure. A short time ago we had the opportunity of studying a case of congestive heart failure in which there was no valvular lesion, hypertension nor kidney disease. At autopsy this case showed sufficient myocardial involvement by tuberculosis to explain the clinical findings in the patient. This and the three following cases are presented to bring attention to tuberculous myocarditis as primary cause of congestive heart failure and to the frequency of tuberculosis involving the heart muscle.

Case Reports

Case 1: History: This patient, a colored woman aged 27, was admitted to the hospital because of dyspnoea and a productive cough of two months' duration. About two years prior to admission she had migratory joint pains which eventually involved most of her joints and at this time had some fever. These symptoms lasted about three months but at no time was she forced to go to bed. For the year preceding admission she had occasional joint pains. Exertional dyspnoea, night sweats and anorexia developed about six months before admission and during this period there was a weight loss of about 9 kilograms. Her symptoms became progressively worse, four months later she developed a cough productive of a white frothy sputum, and entered the hospital in congestive heart failure.

Examination: She was orthopnoeic and had a productive cough. There were moist râles in both lungs and some engorgement of the neck veins. The heart was enlarged and a systolic murmur was heard at the apex. The liver extended 3 cm. below the costal border and there was shifting dulness in both flanks. The haemoglobin was 11.6 gm. and the red count was 3,610,000. The white count was 4,400 with 73 per cent polymorphonuclear neutrophiles, 4 per

[1] From the Department of Pathology, Duke University School of Medicine, Durham, North Carolina.

cent large lymphocytes, 16 per cent small, 2 per cent eosinophiles and 5 per cent monocytes. The sputum gave a one-plus benzidine reaction and contained no acid-fast bacilli. The blood Wassermann, Kahn and the tuberculin reaction were negative. The electrocardiographic record was consistent with myocardial damage and the sinus rhythm was normal. The roentgenograph showed a small mass in the upper mediastinum to the right of the aorta. The patient showed no response to therapy and died thirty-four days after admission.

Autopsy: Anatomical diagnosis: Miliary tuberculosis, diffuse. Tuberculous myocarditis with extensive scarring. Tuberculous lymphadenitis of mediastinal, hilar and cervical nodes. Mural thrombus. Cardiac dilation; chronic passive congestion of lungs and liver. Pulmonary haemorrhagic infarcts. Ascites (1,500 cc.). Pleural effusion, bilateral (500 cc.).

The autopsy was performed two hours after death. The heart weighed 320 gm. and all its chambers were greatly dilated. There was a very slight roughening of the epicardium but no adherence to the parietal pericardium. Scattered throughout the myocardium, especially in the ventricular walls, was a fine patchy scarring. None of these scars were more than 2.5 mm. in diameter. The endocardium had no lesions except on the anterolateral portion of the left ventricle where there was a fresh mural thrombus. The valve cusps were thin without thickening, ulcerations, or vegetations. No gross lesions were seen in the main or subsidiary branches of the coronary arteries. A few firm, white, discrete miliary lesions about 1 mm. in diameter were present in the upper lobe of the right lung. No caseous tubercle was found. The mediastinal, hilar and anterior deep cervical lymph nodes were greatly enlarged. These nodes were discrete and their cut surface had an opalescent, yellow appearance. No caseous areas were found, although there was some tendency to appear nodular. The only lesions found in the other viscera were those associated with chronic passive congestion.

Microscopical findings: The myocardium showed such an extensive patchy fibrosis that there appeared to be more fibrous tissue than heart muscle. The myofibrils outside the fibrotic areas did not appear damaged. The histological picture in the areas of fibrosis was varied; in some parts there was adult fibrous tissue, in others young fibrous tissue and a lymphocytic infiltration (figure 1). In some sections the fibrosis extended from the endocardium to the epicardium. Scattered throughout the heart were numerous tubercles. These were characterized by a collection of round cells and one or two giant cells of the Langhan's type (figure 3). The tubercles were widely distributed and not concentrated close to either the pericardium or endocardium. There was a vascular change in the fibrotic areas. Here the small branches of the coronary arteries had a proliferation of the intima which caused some narrowing of the lumen (figure 1). This change was apparently limited to the fibrotic areas. The

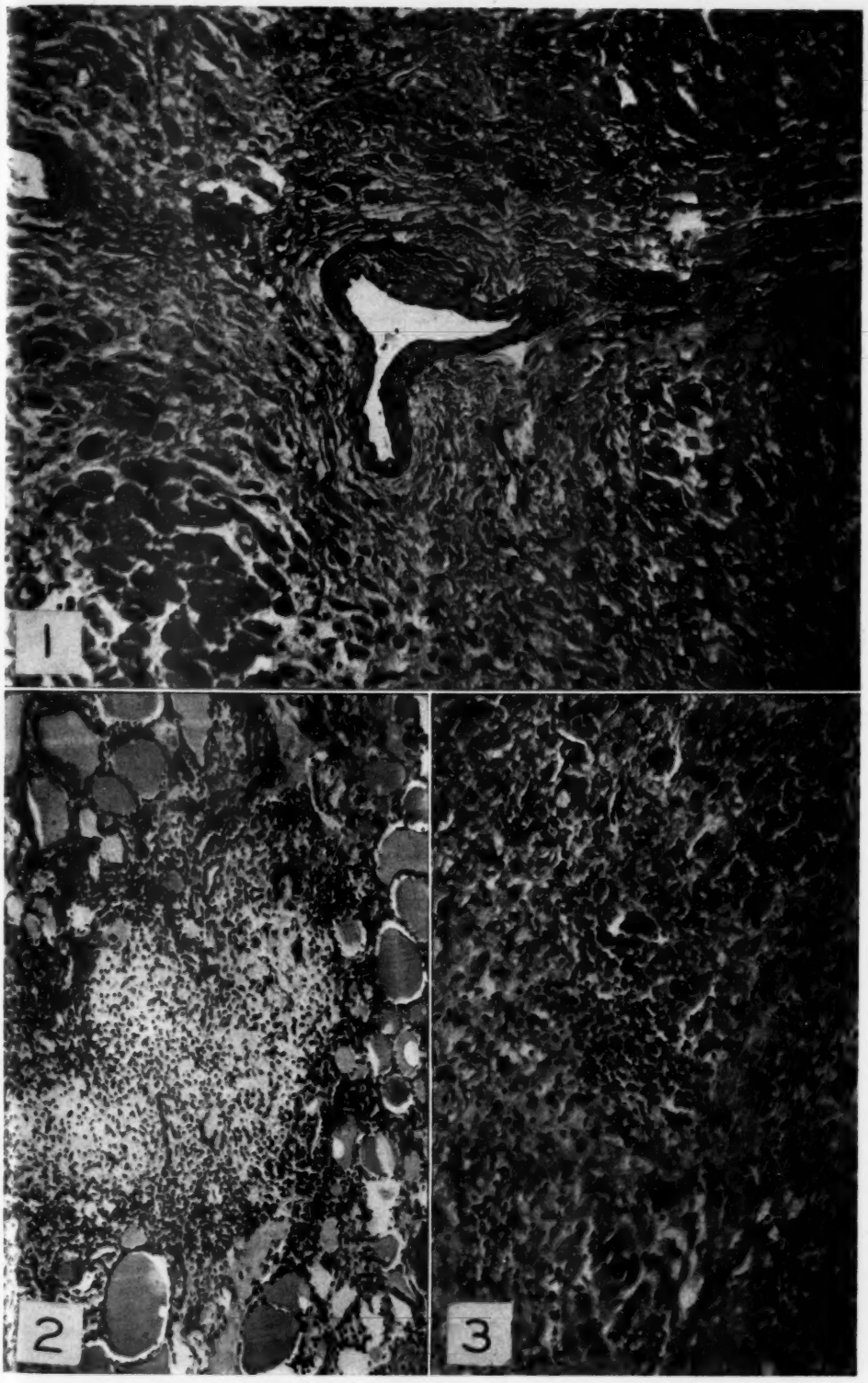

PLATE 1

FIG. 1. Section showing scarring of myocardium and intimal proliferation of small branch of coronary artery (case 1). Hematoxylin-eosin stain. × 120

FIG. 2. Section of tubercle in thyroid (case 1) to show type of lesions in the viscera. Hematoxylin-eosin stain. × 120

FIG. 3. Section of myocardial tubercle (case 1). Hematoxylin-eosin stain. × 120

enlarged lymph nodes had the lymphoid tissue replaced by tubercles with much fibrosis. There were miliary tubercles in the lungs, liver, spleen, kidneys and thyroid. Those in the four latter organs were younger than those in the heart, lung and lymph nodes (figure 2).

Case 2: History: A 26 year old colored female entered with a diagnosis of polyhydramnios or multiple pregnancy of eight months' duration. Her mother had died of tuberculosis six years ago and one sister had tuberculosis. The patient's pregnancy had been uncomplicated until three weeks before admission when her abdomen began to swell and cause some pain. An abscess near the anus was drained two weeks before. There was a harsh systolic murmur over the base of the heart. The abdomen was distended and the fundus was 36 cm. above the pubic bone. The position and presentation of the foetus could not be made out. The accessory clinical data were not unusual.

A premature infant was delivered three days after admission. The infant lived six hours and at autopsy was found to have miliary tuberculosis. A chest X-ray film of the mother three days later showed pulmonary miliary tuberculosis. Then her neck became stiff and the spinal fluid cell count was 1,424 with 97 per cent lymphocytes. Death occurred nine days after admission.

Autopsy: Anatomical diagnosis: Pulmonary tuberculosis (primary caseous tubercle, left lung). Generalized disseminated tuberculosis with tubercles in endocardium and myocardium. Tuberculous glomerulonecrosis. Tubercles of brain with extension to meninges. Tuberculous meningitis. Peritoneal adhesions. Tuberculous endometritis and myometritis.

Autopsy was performed thirty hours after death. The heart had an endocardial tubercle just below the right cusp of the aortic valve. Scattered throughout the myocardium especially in the left ventricle were numerous gray points 1 or 2 mm. in diameter. The remainder of the organs showed an acute disseminated tuberculosis, with a primary caseous node in the left upper lobe.

Microscopical findings: The only myocardial involvement was associated with the endocardial tubercle. The endocardium at this point was caseous. Beneath the caseous area and extending into the myocardium were giant cells and collections of lymphocytes. There was very little destruction of myocardium. It appeared that the oldest or at least the most rapidly progressing lesion was in the endocardium. Tubercle bacilli were observed in many of the lesions in various organs but none were seen in the heart muscle.

Case 3: History: A 25 year old colored male entered Lincoln Hospital, Durham, complaining of generalized headache of a few weeks' duration. The only available history was that he had been feeling badly for some time. The examination showed a stiff neck and loss of superficial and deep reflexes. The accessory clinical data were not unusual.

Autopsy: Anatomical diagnosis: Tuberculous hilar lymphadenitis with direct extension into pericardium. Tuberculous myocarditis and endocarditis with rupture into right atrium. Generalized miliary tuberculosis of lungs and viscera. Tuberculous meningitis. Tuberculosis of skin (pubic region). Ulceration of oesophagus with haemorrhage. Pleural adhesions. Acute appendicitis.

The autopsy was performed thirty-six hours after death. The heart with the adherent and greatly thickened pericardium weighed 560 gm. There were numerous areas of caseation in the pericardium. In the wall of the right atrium just above the attachment of the tricuspid valve was a caseous mass 2 x 1.5 x 2 cm. in diameter. This appeared to be an extension of the pericardial lesion, through the atrium to a point of ulceration on the endocardium. There were large caseous tracheobronchial lymph nodes. The remainder of the organs showed an acute disseminated tuberculosis.

Microscopical findings: There was one large tubercle in the myocardium. This was a large irregular caseous lesion in the atrial wall, surrounded by lymphocytes and rare giant cells. The small branches of the coronary arteries in this region showed an intimal proliferation more extensive than was present in any of the other cases. Tubercle bacilli were seen in the lungs of this case but not in the myocardial lesion.

Case 4: History: A 34 year old colored female entered complaining of weakness, headache, hacking cough and loss of weight. These symptoms were first noticed four years previously and were slowly progressive. There were coarse, moist râles over the entire left lung. The heart and aorta were shifted to the left. The only accessory clinical findings that varied from the normal was a haemoglobin of 12.5 gm. or 80.1 per cent with a red count of 4,200,000. The blood Wassermann was four-plus. She was in the hospital seven days and before death developed an acute circulatory failure from which she never completely recovered.

Autopsy: Anatomical diagnosis: Chronic fibroid pulmonary tuberculosis, with cavity formation, left. Pneumothorax and atelectasis of lung, left. Thrombosis of branch of left pulmonary artery. Compensatory emphysema of right lung. Healed tubercle, right lower lobe. Localized organizing lobular pneumonia of lower right lobe (near hilum). Focal necrosis in liver (fresh tubercles ?). Dilatation and hypertrophy of right heart. Extensive tuberculous myocarditis. Cystitis cystica. Scarring of kidneys.

The autopsy was performed thirteen hours after death. Aside from the extensive tuberculosis of the left lung, the most interesting change was in the heart. The right ventricle was hypertrophied and dilated but the left ventricle showed neither of these changes. Throughout the left ventricular myocardium were numerous yellow patches a few millimetres in diameter. A few similar

lesions were present in the right ventricle. There was a fibrinous pericarditis over the right ventricle.

Microscopical findings: Scattered through the myocardium were collections of round cells and giant cells, but no areas of caseation. In the involved areas there was some replacement of the myofibrils by fibrous tissue. There was an intimal proliferation in the small branches of the coronaries similar to that seen in case 1, but the involvement of the epicardium was much greater. No tubercle bacilli were found in this case. The histological appearance of the heart closely resembled case 1.

DISCUSSION

The rarity of tuberculous myocarditis is difficult to explain. Since the lungs are the commonest site for tuberculous infection and the heart may be reached from the lungs either by contiguous tissues or by retrograde lymphatic extension, this would lead one to think that myocardial involvement might occur more frequently. That tuberculous myocarditis is rare is indicated by the report of Norris (1) and the statistics quoted by Horn and Saphir (2). Even with tuberculous pericarditis or endocarditis significant involvement of the myocardium is uncommon. When Baker (3) reported the series of 6 cases of endocarditis he observed only one case of significant involvement of the myocardium and this apparently preceded the endocardial lesion.

Tuberculous myocarditis may be classified as three types: nodular, miliary and diffuse infiltrative (2, 4). In the pathogenesis of this disease three possible routes must be considered. These are by blood-stream, by retrograde lymphatic extension, and by contiguous tissues. In the four cases presented here at least two of these routes appear to have been utilized. In cases 1 and 4 with the diffuse involvement of the myocardium and the small amount of pericarditis in relation to myocarditis, the blood-stream appears to be the most logical route. In case 3 where there is a heavy pericarditis and a large nodule in the atrial wall with no other apparent myocardial involvement, retrograde lymphatic extension is the most likely, since the pericardium was not adherent to the involved lung. Case 2 has but little myocardial involvement but in consideration of the rest of the case the blood-stream seems the most likely route.

The four cases in this report are logically placed in two groups. In cases 1 and 4 the myocardial tuberculosis is one of the lesions of greatest significance while in cases 2 and 3 it is incidental. Case 1 is of even more interest clinically and pathologically because all of the patient's symptoms were referable to the failing heart. The important feature

of the cardiac involvement in cases 2 and 3 is that the ulceration through the endocardium is an excellent means of wide dissemination.

In case 1 the differential diagnosis is important since no acid-fast bacilli were found. Syphilis can be eliminated by the absence of spirochetes and a negative blood Wassermann and Kahn. Although syphilis might cause similar lesions, a syphilitic process so active should have a positive Wassermann reaction. Rheumatic fever should also be considered. The absence of Aschoff bodies and the character of the extracardiac lesions are not consistent with rheumatic fever. An obscure vascular lesion might cause this myocardial fibrosis. The coronary arteries and arterioles were examined carefully both grossly and microscopically and no lesions other than some intimal proliferation were found. This is consistent with the lesions described in myocardial tuberculosis (4, 5), and those seen here in cases 3 and 4. This is a case of myocardial tuberculosis because the heart and the remaining viscera contain lesions characteristic of tuberculosis, and the lesions found are not consistent with other known disease processes. The negative tuberculin is not contradictory because the patient's allergic reactive ability was probably abolished.

The fact that acid-fast microörganisms were not found prevents proving absolutely that this is a case of tuberculosis. Since the lesions in the heart and elsewhere are histologically characteristic of tuberculosis and no other microörganism could be demonstrated in the bacterial stains, this case may be considered tuberculosis. Although an obscure or unknown granulomatous disease is not excluded, the evidence favors a diagnosis of tuberculosis.

Tuberculosis involving the heart may cause death by more than one mechanism. In tuberculosis of the endocardium the same results may occur that are to be expected in any bacterial endocarditis. Tuberculous pericarditis may cause death by tamponade. When the myocardium is the site of the infection death may result primarily from myocardial failure. Another potential factor to consider is present in case 3. This is the possibility of rupture through a caseous area that extends from an intracardiac chamber to the pericardial cavity. This could result in sudden death due to tamponade.

SUMMARY

A case of congestive heart failure due to myocardial tuberculosis is presented, along with three other cases of tuberculous involvement of

the myocardium. In one of these three patients there was sufficient damage to the heart muscle to cause signs of cardiac insufficiency. The importance of case 1 is the demonstration that tuberculosis can involve the myocardium to such an extent that congestive heart failure may occur in the absence of clinical manifestations of tuberculosis of the pericardium or other viscera. Therefore, in a case of congestive heart failure of obscure aetiology tuberculous myocarditis should be carefully considered in the differential diagnosis.

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SPONTANEOUS LYSIS OF TUBERCLE BACILLI ON ARTIFICIAL CULTURE MEDIA II[1]

WILLIAM STEENKEN, JR.

From the time of the discovery of the tubercle bacillus observers have recognized that cultures of this microörganism tend to exhibit modifications of the usual growth form and a loss of initial virulence. Various causes have been suspected, but none has been proved. Modern methods of culture have demonstrated that under certain conditions this microörganism, like many others, will dissociate into two distinct forms of growth, the one manifesting full virulence (Rv or Sv), and the other (Ra or Sa), so attenuated that it produces little or no progressive cellular reaction. Previously reported experiments (1) have demonstrated that in old cultures of certain virulent strains a spontaneous liquefaction of the colonies took place after a period of three or four months' incubation at 37.5°C. and that subsequently new colonies composed of low-virulent microörganisms developed upon the liquefied areas. If it could be shown that more cultures of human type underwent similar changes and that the ultimate Ra colonies produced from different parent strains had identical or similar properties of growth and virulence, an explanation for spontaneous loss of virulence might be found.

The present communication reports a repetition of the original investigation on nine more strains of human type tubercle bacilli; one of them was the well known H37 isolated thirty-two years ago, and the other eight (table 1) were freshly recovered from sputum, spinal fluid and other tuberculous lesions. It also describes the attempts to define the conditions under which the Ra colonies developed.

EXPERIMENTAL DATA

Culture characteristics: A transplant of the previously dissociated (2) Rv variant of the human type culture H37 was made on gentian-violet egg medium of pH 6.2 and allowed to remain in the incubator at 37.5°C. for four months. Examination at the end of two months showed that the centre of some of the colonies had begun to soften (figure 1) which

[1] From the Research and Clinical Laboratory, Trudeau Sanatorium, Trudeau, New York.

was followed by liquefaction with complete loss of morphological structure. During the following two months the process spread peripherally until the original colony was destroyed and was replaced by a flat, viscid mass. In this mass new nodular growths (figure 1a) made their ap-

TABLE 1

Source of cultures used

NUMBER	AGE	SEX	SOURCE
J. H. 6	19 months	Male	Mesenteric lymph nodes obtained at autopsy
J. H. 10	8 months	Male	Spinal fluid
J. H. 16	3½ years	Male	Pus from flank abscess
J. H. 17	3½ years	Male	Spinal fluid
T. S. 30	23 years	Female	Sputum, duration 14 months. Productive, cavernous, active, progressive. Gaffky IX or X always
T. S. 4	44 years	Male	Sputum, duration 2+ years. Brother died of tuberculosis. Productive, chronic, cavernous, progressive. High Gaffky, V to X always
T. S. 12	36 years	Male	Sputum, duration 7 years. Active, exudative, cavity, largely productive, progressive. High Gaffky, VIII to X always. Laryngitis
T. S. 13		Male	Sputum
H 37	19 years	Male	Isolated by Dr. E. R. Baldwin in 1905 from patient suffering from chronic pulmonary tuberculosis

J. H. = Johns Hopkins, Department of Pediatrics.
T. S. = Trudeau Sanatorium.

FIG. 1. Lyzed Rv colony; gentian-violet egg medium, pH 6.1; 150 days' growth. (a) Secondary resistant growth. ×2

FIG. 2. Lyzed Rv colony; gentian-violet egg medium, pH 6.1; 200 days' growth. (a) Secondary resistant growth. ×2

FIG. 3. Resistant growth; gentian-violet egg medium, pH 6.1; 120 days' growth. (b) Early colony forms of resistant growth. (a) Fully matured resistant colony. ×5

FIG. 4. Resistant colony: Lateral section 6 micra, Ziehl-Neelsen stain; 120 days' growth. ×20. (a) Non-acid-fast mucoid substance.

FIG. 5. Resistant colonies, pure culture; gentian-violet egg medium, pH 6.1; 85 days. ×2

FIG. 6. Lyzed Rv growth; gentian-violet egg medium, pH 6.1; 200 days' growth. (a) Resistant growth. ×5

FIG. 7. Rv and resistant colonies; gentian-violet egg medium, pH 6.1; 150 days' growth. (a) Resistant growth. ×5

FIG. 8. Resistant colonies, pure culture; gentian-violet egg medium, pH 6.1; 85 days' growth. ×2

FIG. 9. (a) Resistant colony, outer surface; gentian-violet egg medium, pH 6.1; 120 days' growth. ×2. (b) Resistant colony, under surface; gentian-violet egg medium, pH 6.1; 120 days' growth. ×2

FIG. 10. (c) Resistant colony, outer surface; gentian-violet egg medium, pH 6.1; 85 days' growth. ×2. (d) Resistant colony, under surface; gentian-violet egg medium, pH 6.1; 85 days' growth. ×2

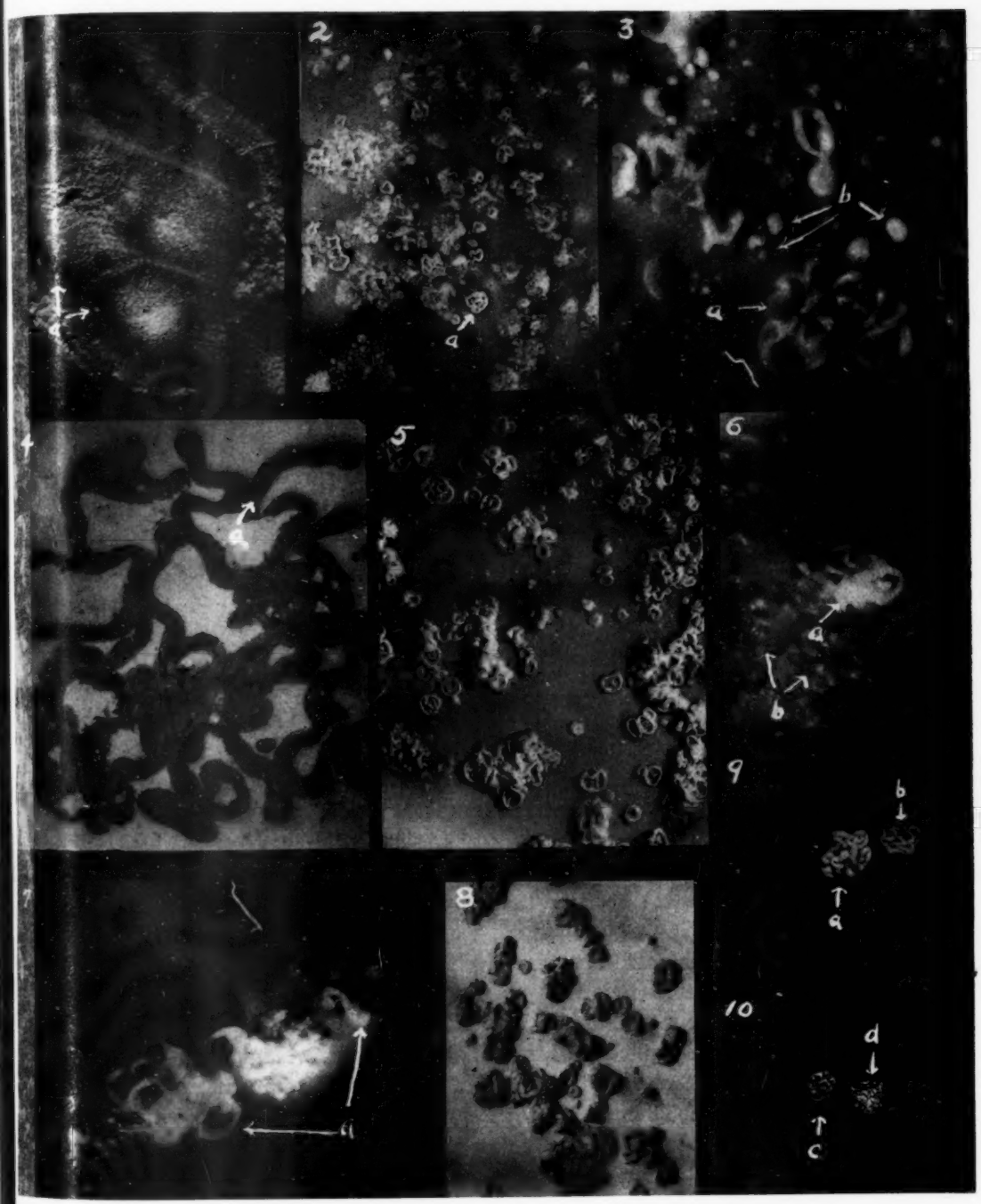

PLATE 1

pearance which increased in size and finally assumed the convoluted structure illustrated in figures 2a, 3a and 6a. The new colonies were not attacked and liquefied on aging, but were apparently stable. Hence they have been termed resistant colonies.

Subcultures from these new colonies produced small nodular, moist ones like those shown in figure 3b. As the latter continued to grow they passed through the phase shown in figures 5 and 8 and finally assumed the mature form, a large raised colony composed of smooth worm-like convolutions shown in figures 3a and 7a. Transplants onto Petragnani's, Hohn's and Steenken and Smith's (3) media grew well.

Subcultures of the lysed material on gentian-violet egg and the other media used for the resistant colonies, all failed to produce growth within a period of two months. Stained smears (figure 13) showed irregular microörganisms which were only partially acid-fast. It was therefore assumed that the bacilli had died in such areas.

Further study of the resistant colonies demonstrated that, between the surface of the convolutions and the culture medium, there was a layer of thick mucoid fluid which did not increase in amount. Growth took place on the surface and, as more bacteria formed, they piled up to produce the worm-like convolutions. (Figures 9a and 10c, outer surface of colonies.) (Figures 9b and 10d, under surface of colonies.)

The reaction in areas of liquefaction was determined by removing small blocks of medium and it was found that the pH varied between 4.2 and 4.6. It is most surprising that the resistant colonies should be able to develop on such an acid soil.

Some of the resistant colonies were fixed in alcohol, embedded in paraffin and sectioned to demonstrate the relationships between the mucoid fluid and the colony. Lateral sections stained by the Ziehl-Neelsen method (figure 4) showed that the centre of the colony and all the sulci (figure 4a) between the convolutions were filled by a homogeneous, non-acid-fast coagulum. As the periphery was approached, increasing intense acid-fastness developed. At the outer border were typical acid-fast bacteria.

Smears of the resistant colonies stained by the Ziehl-Neelsen method revealed marked pleomorphism of the component microörganisms. (Figures 11, 12, 14, 15.) There were minute granules, only some of which were acid-fast. There were larger round or ovoid bodies of varying degrees of acid-fastness. There were well developed bacillary forms with large deeply stained acid-fast granules.

Animal inoculations: To demonstrate whether the lysed colony contained any living microörganisms, intratesticular inoculations of 5 mg. were made into each of two guinea pigs. The material was collected from a gentian-violet plate incubated for 200 days (figure 6b). Thirty days after injection the animals were skin tested with tuberculin and showed 12 by 12 mm. areas of erythema and induration. Subsequent

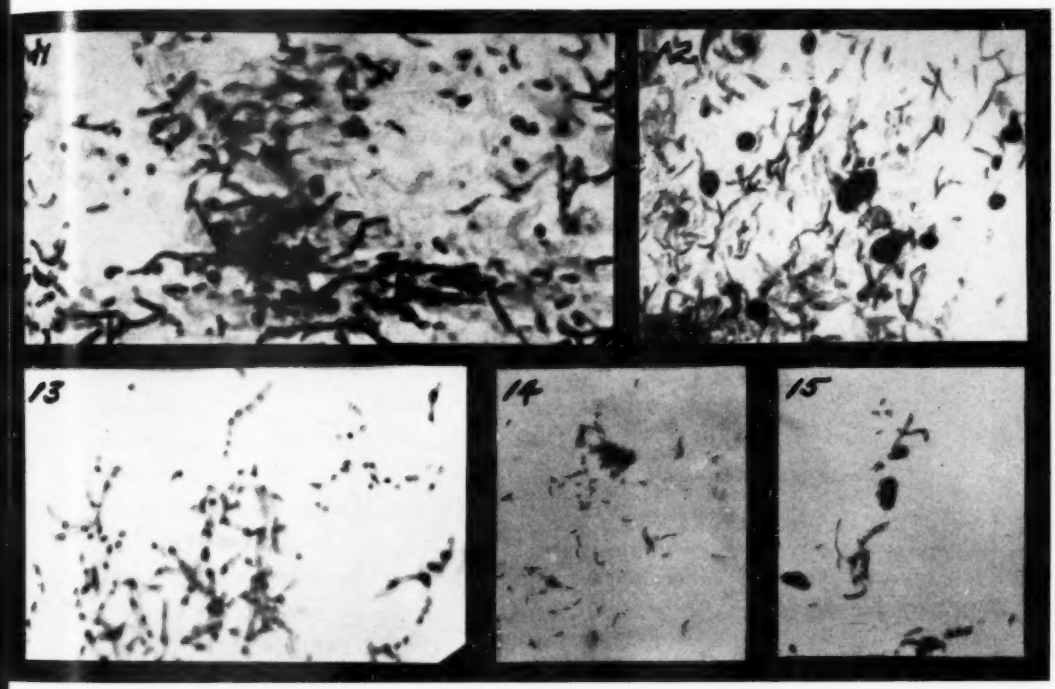

PLATE 2

FIGS. 11, 12, 14 & 15. Resistant growth; fixed smear from 150 days' culture, gentian-violet egg medium, pH 6.1; Ziehl-Neelsen stain. From ×600 to ×865.

FIG. 13. Rv growth; lyzed area; fixed smear from 150 days' culture; gentian-violet egg medium, pH 6.1; Ziehl-Neelsen stain. ×865.

tests repeated during the next five months indicated no decrease in skin hypersensitiveness. The animals were killed at the end of this period and showed no evidence of tuberculosis. There was slight atrophy of the testes, but tubercle bacilli could not be demonstrated.

Control tests with 5 mg. of microörganisms from a resistant colony (figure 6a) in the same culture were made in the same manner. The thirty-day tuberculin tests caused slightly more reaction, the area of

erythema and induration measuring 15 by 15 mm. in diameter, but just before the animals were killed it was of the same intensity as that in the previous group. Autopsy disclosed no evidence of tuberculosis in either animal.

Further animal inoculations were made with microörganisms from resistant colonies to be certain whether they were even capable of producing tuberculosis.

A: Four guinea pigs were inoculated intratesticulary with 5 mg. of bacilli from resistant colonies; all developed positive tuberculin reactions. The first died of pneumonia after 21 days; the others were killed after 35, 51 and 65 days respectively, and none revealed macroscopical evidence of tuberculosis at autopsy.

B: Two guinea pigs were inoculated intraperitoneally with 5 mg. of a forty-day old colony of the resistant type. Without killing the animals exudate was removed from the abdominal cavity at intervals of 24, 48, 72 and 96 hours after inoculation and smears were stained to observe the bacteria. The number of microörganisms, both in free state and inside of phagocytes, decreased progressively during the period of observation. The proportion of acid-fast bacillary forms in the growth had not increased during residence in the animal body. Most of the microorganisms consisted of the ovoid bodies and the fine granules noted above.

C: These two guinea pigs reacted positively to tuberculin on the 32nd day and thereafter until killed. The first was sacrificed on the 60th day and the other on the 330th day after infection. Neither showed macroscopical evidence of tuberculosis.

D: Repeated intratesticular injection of the same animal likewise failed to produce infection. Two guinea pigs were inoculated into the right testis every other day with 5 mg. of bacilli from resistant colonies until each had received a total of 45 mg. Thirty days later both exhibited marked reactions to intracutaneous injections of tuberculin which persisted throughout their lives. The first guinea pig was killed 65 days after completing the injections, but showed no macroscopical evidence of tuberculosis. Its right testis was atrophied and smears of its tissue revealed the usual ovoid acid-fast bodies and granular material. In the other animal killed after 240 days, these microörganisms had disappeared, a few adhesions marking the site of injections.

E: Rapid passage through five different guinea pigs not only failed to demonstrate any enhancement of virulence, but the microörganisms

were finally so reduced in numbers that skin hypersensitiveness failed to develop in the last member of the series.

Two guinea pigs were injected intratesticularly with 10 mg. of bacilli from resistant colonies grown on gentian-violet egg medium for 40 days. Their skin reacted to tuberculin after 15 days. On the 17th day the right testis of one was removed aseptically, triturated in a mortar and reinoculated into the testes of two more animals. The process was continued at 16-day intervals over a period of 85 days. All were given tuberculin tests 150 days after injection and the first four passage animals reacted with 10 by 10 mm. areas of erythema and induration. The last two showed no response. Autopsy revealed atrophied testes in the first four and no lesion in the last pair.

All of the tests previously reported for strain H37 were repeated with J.H. 6 with identical results. The remaining seven cultures were allowed to age and as they developed the same degenerative changes followed by the appearance of new resistant colonies, only the virulence tests were repeated. Inoculation of the latter invariably produced skin hypersensitiveness without gross evidence of tuberculosis.

The nature of the degenerative changes occurring in old cultures was uncertain; apparently there had been lysis or autolysis of the microorganisms to produce the marked destruction of the original colony. Was it due to a ferment liberated by living or by dead microörganisms? The highly acid reaction of the medium indicated that a lowered hydrogen ion concentration was an important feature. It seemed likely that a Berkefeld filtrate of the degenerated colonies might contain the lytic principle and that this should manifest its action upon heat-killed or virulent Rv variants of the H37 strain in a medium of the proper reaction. If the process were one of autolysis due to enzymes, the dead microörganisms should be broken down. If lysis occurred, the living microörganisms should be broken down.

Accordingly the following tests were made:

A filtrate of a 150-day liquefying Rv culture was made by triturating both the microörganisms and the solid medium upon which they were growing in a sterile mortar with the addition of about 100 cc. of physiological salt solution to facilitate grinding. The entire content of the mortar was transferred to a ball mill and ground continuously for 6 hours. The homogeneous fluid was filtered first through paper and then through a "W" Berkefeld filter.

TABLE 2

pH	LIVING MICROÖRGANISMS	DEAD MICROÖRGANISMS	CONTROLS	
			Living Microörganisms	Dead Microörganisms
2.2	Few faintly stained bacilli	Many intact bacilli and few faintly stained	Few faintly stained bacilli	Many intact bacilli and few faintly stained
2.6	Few faintly stained bacilli	Many intact bacilli and few faintly stained	Few faintly stained bacilli	Many intact bacilli and few faintly stained
3.0	Few faintly stained bacilli	Many intact bacilli and few faintly stained	Few faintly stained bacilli	Many intact bacilli and few faintly stained
3.4	Many eroded and faintly stained bacilli	Many intact bacilli and few faintly stained	Few faintly stained bacilli	Many intact bacilli and few faintly stained
3.8	Many eroded and faintly stained bacilli	Many intact bacilli and few faintly stained	Few faintly stained bacilli	Many intact bacilli and few faintly stained
4.0	Very few intact bacilli	Practically all intact acid-fast bacilli	Few faintly stained bacilli	Many intact bacilli and few faintly stained
4.2	Very few intact bacilli	Practically all intact acid-fast bacilli	Few faintly stained bacilli	Many intact bacilli and few faintly stained
4.4	Very few intact bacilli	Practically all intact acid-fast bacilli	Practically all intact bacilli	Practically all intact bacilli
4.6	Very few intact bacilli	Practically all intact acid-fast bacilli	Practically all intact bacilli	Practically all intact bacilli
5.0	Very few intact bacilli	Practically all intact acid-fast bacilli	Practically all intact bacilli	Practically all intact bacilli
5.4	Very few intact bacilli	Practically all intact acid-fast bacilli	Practically all intact bacilli	Practically all intact bacilli
5.8	Very few intact bacilli	Practically all intact acid-fast bacilli	Practically all intact bacilli	Practically all intact bacilli
6.2	Growth started; deep seated; bacilli intact	Practically all intact acid-fast bacilli	Practically all intact bacilli	Practically all intact bacilli

6.6	Growth started; deep seated; bacilli intact	Practically all intact acid-fast bacilli	Practically all intact bacilli	Practically all intact bacilli
7.0	Growth on surface; bacilli intact	Practically all intact acid-fast bacilli	Practically all intact bacilli	Practically all intact bacilli
7.4	Growth on surface; bacilli intact	Practically all intact acid-fast bacilli	Practically all intact bacilli	Practically all intact bacilli
7.8	Scant growth on surface; bacilli intact	Practically all intact acid-fast bacilli	Bacilli swollen and intact	Practically all intact bacilli
8.0	Bacilli swollen and intact	Practically all intact acid-fast bacilli	Bacilli swollen and intact	Practically all intact bacilli

A uniform suspension of Rv variant of H37 tubercle bacilli was prepared in physiological salt solution of pH 7.0. Several colonies were triturated in a sterile mortar adding physiological salt solution of pH 7.0 as necessary. When homogeneous the material was transferred to a test tube where it was allowed to settle for one hour to remove large clumps. At the expiration of this period the supernatant fluid was pipetted off and the quantity of microörganisms it contained was estimated by the dry weight method. Sufficient salt solution was added to bring the final concentration to 1 mg. per cc. This bacterial suspension was divided into two parts. One of them was heated in a bath of boiling water for one hour to kill the microörganisms; the other was untreated.

A series of Mellvaines (4) standard buffer solution whose pH varied from 2.2 to 8.0 was prepared and 7 cc. of each was placed in 4 test tubes and sterilized. To half of the tubes of buffer solution 1 cc. of the filtrate was added and the mixture was incubated at 37.5°C. overnight to be certain of their sterility. The other half which received no filtrate was kept for the controls. On the following morning 0.5 cc. or 0.5 mg. of suspension of both living and heat-killed Rv tubercle bacilli were added to two tubes of each of the buffer solution tubes. A control series without filtrate was also prepared. All the tubes were placed in the incubator and shaken thoroughly every day during a period of 150 days. Every two weeks a loop of suspension was withdrawn from each tube, spread on a slide and stained by the Ziehl-Neelsen method.

At the end of the first two weeks the microörganisms in all tubes were practically unchanged. After one month the living microörganisms in buffers of pH 4.2 to 5.0 plus filtrate showed marked swelling and degeneration. The heat-killed microörganisms were intact at this period and remained so up to 150 days at which time the results were tabulated as shown in table 2.

Table 2 shows two distinct types of reaction taking place. If we compare the microörganisms of the living with those of the heat-killed series from pH 2.2 to 4.0, it will be noted that they are almost identical morphologically. On the other hand, when the living are compared with those of the heat-killed series, from pH 4.2 to pH 5.8, there is marked morphological difference, the living being more susceptible to a definite lytic action which seems to be active within that pH range. Below pH 4.0 the phenomenon is probably autolysis as it has the property of destroying the dead microörganisms. From pH 5.8 to 8.0, both the living and dead microörganisms remain intact. It is quite probable that

if the pH were increased far above 8.0 there would be another zone of autolysis.

Also it is interesting to note that growth took place in the tubes from pH 6.2 to 7.8, some starting from the bottom and some on the surface.

When the control series is analyzed it will be noted that between the pH range of 2.2 to 4.2 the results are practically the same as in the other series, but from pH 4.4 to 7.4 they differ, there being no morphological difference between the living and dead bacilli. This would seem to demonstrate that there is a specific lytic principle active in the filtrate between the pH range of 4.2 and 5.8. No growth appeared in any of the control tubes and this is probably due to a lack of nutritive material which was present in the Berkefeld filtrate that was added to the other series.

Table 3 demonstrates the effect of the combination of buffer and filtrate upon the viability and virulence of the H37 Rv variant at the end of 150 days' incubation at 37.5°C.

At this point the question might be raised as to whether the resistant type colony is present along with the Rv variant at all times and whether it will propagate only when the pH of the medium is optimum for its growth. To be sure that this was not the case, single cell isolations were made using the Chambers dilution method for isolating single cells and the resulting colony growth was planted on gentian-violet egg media and plain egg media, starting with pH 3.0 and increasing 0.2 of a pH up to pH 8.4. Colony morphology of the Rv variant could be made to vary with the change in pH, but the virulence remained constant, as shown by positive inoculations.

It seems quite obvious that pH is not the sole factor in the development of the resistant type of colony, but that the metabolic products or lytic principle itself is responsible for a mutation or reversion that takes place within the Rv variant. Never have these resistant colonies appeared elsewhere than upon these lyzed colonies. This tends to the explanation that mutation or reversion is brought about as mentioned above.

All cultures used in this experiment were isolated by sodium hydroxide or sulphuric acid digestion methods directly from pathological specimens. Neither of these methods had any effect upon the type of colonies or the virulence of the microörganisms for guinea pigs. In the case of several spinal fluids which were positive for tubercle bacilli on cultivation and negative for secondary microörganisms, one-third of the total amount of each was placed on gentian-violet egg media of pH 6.5 and one-third

was digested with sodium hydroxide and planted on gentian-violet egg media of pH 6.5. The remaining third was digested with sulphuric acid and placed on the same media. None of these three plates revealed other than the Rv colonies of marked virulence.

A more extensive experiment (Steenken and Smith (5)), using both methods of digestion and various media of different pH for cultivation,

TABLE 3

pH	NUMBER OF GUINEA PIG	SKIN TEST 30 DAYS AFTER INOCULATION	SKIN TEST 60 DAYS AFTER INOCULATION	DEGREE OF TUBERCULOSIS	DAYS OF LIFE	CULTURE
2.2 to 5.4	1 to 24	0	0	0	300	0
5.8	25	0	0	0	300	0
	26	0	0			0
6.2	27	+	+	+	180	+
	28	+	+			+
6.6	29	+	+	+	167	+
	30	+	+			+
7.0	31	+	+	+	205	+
	32	+	+			+
7.4	33	+	+	+	170	+
	34	+	+			+
7.8	35	+	+	+	165	+
	36	+	+			+
8.0	37	0	0	0	300	0
	38	0	0			0
Rv control	39	+	+	+	71	+
	40	+	+			+

shows quite clearly the effect upon colony morphology of the bacilli from variants of known source.

As to the microscopical morphology of the bacilli from the resistant colonies, it has been observed repeatedly in this experiment that round and ovoid, acid-fast and non-acid-fast bodies, as well as dust-like granules and bacillary forms are present in both young and old cultures.

These large round acid-fast bodies increase in size as the cultures get older. This is more pronounced on the solid media than on the fluid.

The question might be raised as to whether they are contaminations by yeasts or molds. To meet this criticism these cultures were cultured on all laboratory media that are favorable to their growth. None of the media gave growth to any of the large, round acid-fast bodies, or any other type of growth. This tends to prove that they are not yeasts or molds growing in symbiosis with the resistant type colony. These large, round and ovoid acid-fast bodies may be swollen microörganisms which eventually rupture and thereby produce the dust-like appearing bodies that are observed in smear.

When one considers the lag or growth period of the tubercle bacillus as contrasted with that of other bacteria, it is not surprising that the rate of lysis is so slow compared with lysis in them.

It might also be suggested that the cause of loss of virulence of various laboratory strains that are reported is due to faulty technique in the transfer of cultures to fresh media. For instance, many times cultures might be missed in transplanting for several months, that is, no transfer made. This is a sufficient length of time for a marked drop in pH, which in itself has an attenuating effect. Also, the secondary or resistant type of colony might be developing on a culture together with the ordinary growth and when transferred it would be carried to new media. Under these conditions, there would be a predominant number of the avirulent microörganisms. After many generations this avirulent type would proportionately increase and if these tubes were missed for a couple of transfers they would undergo the same change and finally the virulent microörganism would be eliminated. This seems to be the case with BCG as it did not lose its virulence at once. It was a gradual change in virulence which was probably a slow increase in the ratio of Ra to Rv microörganisms, until to date it is practically an Ra strain.

SUMMARY

It has been shown in the preceding pages that ripe cultures of human strains of the Rv variants undergo liquefaction on gentian-violet egg and plain egg media giving rise to a secondary, resistant growth of a different colony and bacillary morphology. The microörganisms from the liquefied area did not produce tuberculosis in the guinea pigs as did the original mother colony. Neither would they grow on any of the media mentioned. However, the secondary resistant type colony, although it did not produce progressive tuberculosis, grew on all of the laboratory media mentioned.

It was observed that the resistant colonies produced skin hyper-

sensitivity in guinea pigs when inoculated intraperitoneally, intratesticularly and subcutaneously, and that this might persist for one year or longer. When the guinea pigs were killed at the end of a year, autopsies showed no macroscopical lesions, except occasionally at the site of injection of the intratesticularly infected animals, and these lesions were generally accompanied by a small amount of fibrosis without any demonstrable acid-fast microörganisms. Early lesions at times were caseous and acid-fast bodies of marked pleomorphisms could be demonstrated.

The above lytic phenomenon is not only inherent in the H37 Rv culture, but has been shown to exist with other Rv variants of human origin. Also all of the cultures used in this experiment were of human origin as proved by the present methods of differentiation.

It has been demonstrated that there is a definite lytic principle in the filtrate of the culture which acts upon the living bacilli within a definite range of pH.

It has also been observed that the bacillary morphology of the resistant colony is markedly different from the Rv variant.

I wish to thank Dr. Oswald T. Avery of The Rockefeller Institute for Medical Research for his many helpful suggestions, also Doctors Baldwin, Gardner and Heise for their interest and encouragement.

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EDITORIAL

Endogenous Reinfection and Primary Complex

Whether endogenous or exogenous reinfection is the more frequent mechanism in the pathogenesis of pulmonary tuberculosis in the adult is still undecided. Both parties in this dispute are probably pretty well in agreement that a direct and convincing proof for one or the other opinion is still lacking. It might, therefore, be of some importance to examine quite closely the findings and conclusions that Doctors Feldman and Baggenstoss (1) present in a notable contribution to this problem, particularly since their work has received further emphasis in an editorial in the Journal of the American Medical Association (2).

Doctors Feldman and Baggenstoss have examined for the presence of viable tubercle bacilli, by cultural methods and by animal inoculation, 103 specimens consisting of primary complexes from 68 individuals who at autopsy did not present gross evidence of active tuberculosis. This work was done with the most reliable methods available. No tubercle bacilli were found, save from one patient. The authors conclude, and the editorial mentioned concurs, that the apparent sterility of the primary complex "suggests that in adults endogenous reinfection is unlikely to occur from lesions of the primary complex."

There can be no reason to doubt the accuracy of the findings: the lesions examined from 67 individuals did not contain viable tubercle bacilli. This is an important finding and justifies fully the authors' statement "that the chronic lesions of tuberculosis undergo spontaneous arrest and that in such lesions living tubercle bacilli can rarely be demonstrated."

But still there are justifiable doubts concerning the immensely important question of the possibility or likelihood of endogenous reinfection.

(1) *Were all the lesions examined primary complexes or part of them?* Assuming that all foci examined were of tuberculous origin, the paper does not present any proof for the implicit statement that all (with the five exceptions stated) were primary. Answering a discussion remark, following Doctor Feldman's presentation at the last annual meeting of the American Association of Pathologists and Bacteriologists (3), Doctor Feldman said that the autopsies were done by somebody else and that

he received only the material which was used for the subsequent studies, and that "in the majority of cases we were dealing with what seemed to be old Ghon tubercles." In 41 cases, sections were made from 46 specimens, apparently not primarily to determine the pathological nature of the foci but in order to classify the material as to the histological evidence of activity. It is, or should be, well known that "primary complex" is not a histological diagnosis, but a gross anatomical diagnosis in which the totality of the respiratory organs with the intact topographical relationship of the foci is required evidence which, in its turn, may need histological confirmation. The photomicrographs appended to the paper are not all convincing of the primary nature of the foci; indeed, figures 1, 3, 4 and 6 stimulate further doubt.

(2) *Is the primary complex proper the only possible source of endogenous reinfection?* During the active stage of the primary complex, bacillary disseminations by lymph and blood-stream are a common occurrence. Some of the disseminated bacilli may focalize in the lymphatic drainage system beyond the immediate lymph node component of the primary complex, some may reach the lung through the blood-stream. Such lesions, escapes from the primary complex, may contain viable tubercle bacilli long after the latter has become sterile; these satellite lesions must be considered as potential sources of later endogenous reinfection.

(3) *Should the pathogenesis of reinfection best be studied in persons having no reinfection?* Doctors Feldman and Baggenstoss state, "Evidence of infection with *Mycobacterium tuberculosis* as observed grossly was limited in most instances to well encapsulated caseous or caseocalcareous Ghon tubercles or similarly affected tracheobronchial lymph nodes." It would appear, then, that most foci examined were from individuals who had never had any significant postprimary tuberculosis. With the proof that under these conditions the foci are sterile, the correlative questions arise whether the sterility of the foci is not an important cause of the absence of reinfection lesions and whether individuals with bacilliferous old or primary foci are not frequently reinfected endogenously from such bacillary depots. These questions can obviously not be answered on the basis of the material examined. The questions posed are not presented as a likely hypothesis, but as a missing link in the arguments adduced by Doctors Feldman and Baggenstoss.

The studies discussed here have proved beyond a doubt that tuberculous lesions in humans can heal bacteriologically. This work, executed with flawless technique, is probably the most complete demonstration

of this fact, contradicting the old saying "once tuberculous, always tuberculous." This, I believe, is its real and its great significance. That it proves, or even suggests, the improbability of endogenous reinfection, is reasoning beyond its factual basis.

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THE AMERICAN REVIEW OF TUBERCULOSIS

JOURNAL OF THE NATIONAL TUBERCULOSIS ASSOCIATION

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VOLUME XXXVIII

JULY-DECEMBER, 1938

PUBLISHED MONTHLY

AT MT. ROYAL AND GUILFORD AVENUES, BALTIMORE, MD.

BY THE NATIONAL TUBERCULOSIS ASSOCIATION